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THE RELATION OF TANNIC ACID TO THE LIVER NECROSIS OCCURRING IN BURNS*

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THE phenomena associated with severe burns follow each other in a more or less orderly and well-defined chronologic sequence.[1] Death may result almost immediately from overwhelming trauma. Most burned patients are seen in primary reflex shock, a state of marked vascular vasodilatation caused by fright and pain. Primary reflex shock may blend rapidly and almost imperceptibly with so-called "secondary shock," which, with its increasing capillary permeability and massive fluid shift or loss, may be fatal within forty-eight hours. What we are accustomed to calling "toxemia" ensues; however, the use of the adjective "toxic" to describe a patient in poor condition from undetermined causes is certainly no proof that a toxin exists, and belief in a "toxemia" in burns may well arise from the clinician's bewilderment in the face of potent factors that he cannot readily catalogue. It is interesting that no less than twenty substances purporting to be the "burn toxin" have been listed[2] but no specific histopathology for burns has ever been described. Infection is usually a comparatively late stage in the chronologic sequence; but in three or four days, if severe sepsis develops, it may overshadow the whole clinical picture.

Ten consecutive autopsies recently performed in cases of death from burns at the Hartford Hospital serve to illustrate this sequence of events. Two of these patients died from direct trauma within two to four hours after injury; another died of shock or fluid imbalance eleven hours after the injury; 4 more died of "toxemia" ninety-three to one hundred and twenty hours following the injury; another, admitted late, died of infection one hundred and twenty hours after the injury, a blood culture on admission showing hemolytic streptococci; the last 2 died of complications, 1 fifty-five hours after the accident from the result of an associated cerebral laceration sustained in an airplane crash, and 1 of a cerebral glioma thirty-three days after admission — the glioma was probably the cause of the convulsive seizure during which this patient was burned. The 4 patients who died of "toxemia" are of particular interest, and their cases are briefly presented below because each one exhibited central lobular liver necrosis as an outstanding lesion or as the sole cause of death. Treatment of these patients followed the general principles laid down by one of us[3]: the employment of a tannic acid tub in which a careful débridement was done without an anesthetic, a thin, sterile tan being secured in every case; the tan was subsequently maintained by the use of a tannic acid spray, and for the most part was kept perfectly dry by a current of warm air from a commercial hair drier; intravenous glucose in physiologic saline solution was given in adequate quantities; each patient received whole-blood transfusions; and intranasal oxygen was employed.

CASE REPORTS

CASE 1. R. W. (H. H. 338,316), a 17-year-old boy, was admitted on July 1, 1937. Practically all his clothing had been burned off when a can of gasoline he was holding became ignited from a bystander's cigarette. The burns were estimated to involve not less than five sixths of the entire body surface. The patient was immediately put in a tub of tannic acid solution, the loose skin removed, and the hair shaved. He remained in the tub 4½ hours and, after being transferred to bed, was sprayed repeatedly with a tannic acid solution and immediately dried with a commercial hair drier. Intravenous glucose and three whole-blood transfusions were given. Continuous intranasal oxygen was started 18 hours after admission. The patient was spontaneously responsive during most of his stay in the hospital, but became increasingly restless and irrational after the 63rd hour, when the blood nonprotein nitrogen was 128 mg. per 100 cc. and the hemoglobin 111 per cent. Death occurred 91 hours after admission.

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Autopsy. The body was that of a well-developed and well-nourished boy. At least five sixths of the body surface was covered with a firm, dry tan without evidence of infection. There was marked congestion of the viscera, with scattered petechiae, and blood-tinged fluid was present in the body cavities. There was no ulceration of the duodenal mucosa. The liver weighed 1960 gm. and showed no gross changes. The gall bladder and bile ducts were not unusual.

On microscopic examination, all organs except the liver showed nothing but cloudy swelling and congestion. In the central two thirds of the liver lobule, the parenchymal cells showed a granular, deep-pink-staining cytoplasm in contrast to the relatively normal cells in the peripheral area. Throughout this central zone, the nuclei were slightly enlarged, and there were numerous necrotic foci (Plate 1, *A*). A moderate number of mitoses were present in the peripheral zone (Plate 1, *B*). The sinusoids were distended with blood. There was no leukocytic infiltration.

Comment. This case showed a combination of early liver necrosis and vascular failure. The latter was probably the greater lethal factor.

CASE 2. N. N. (H. H. 357,822), a 23-year-old man, was admitted on August 18, 1938. An electric flash in a transformer room had ignited his clothing. The entire head, the torso to the waistline, both upper extremities and wide patches on both thighs, both anteriorly and posteriorly, were burned. The patient was put in a tub of tannic acid solution and carefully and thoroughly débrided. He remained in the tub 2¼ hours. This treatment was followed by repeated spraying with a tannic acid solution, which was immediately dried with a commercial hair drier. Three transfusions were given, and no gross fluid imbalance was clinically apparent until the last 24 hours of life, when edema of the lower extremities developed. About 2 hours before death, the patient became restless, complained of severe pain in the upper abdomen, and vomited several times. He died 96 hours after admission.

Autopsy. The body was that of a well-developed and moderately overnourished young man. The burned areas were covered by a firm, dry, noninfected tan. The tissues were moist and moderately icteric. A moderate amount (200 cc.) of slightly bloody fluid was present in the body cavities. The viscera showed moderate congestion, with scattered petechiae. The liver weighed 2000 gm., and the cut surface showed a fine mottling, with hemorrhagic points. The gall bladder and biliary ducts were not unusual. No ulceration of the duodenal mucosa was found.

On microscopic examination, except for multiple small thrombi in the lungs and congestion and cloudy swelling of other viscera, significant histologic changes were limited to the liver. The central three fourths of the liver lobules showed extensive hemorrhagic necrosis, with complete disruption of the cords of liver cells (Plate 1, *C*). A few cells in the peripheral region were still intact, and some of these were in mitotic division. A slight diffuse infiltration of polymorphonuclear leukocytes was present throughout, together with a scattering of fat globules. There was no increase in fibrous tissue.

Comment. Although the changes present in this case suggested vascular failure, the picture was dominated by the liver necrosis.

CASE 3. K. W. (H. H. 388,162), a 23-year-old man, was admitted on April 26, 1940. An explosion of illuminating gas had resulted in burns involving the entire face and neck, upper chest, back and both arms except for the palms of the hands. The patient was immediately put in a tub of tannic acid solution, where a thorough débridement was carried out. He remained in the tub for 2¼ hours. After being removed, he was repeatedly sprayed with a tannic acid solution and immediately dried with a commercial hair drier. Intravenous glucose and two whole-blood transfusions were given. For the first 72 hours, the general condition remained satisfactory, and the patient sat up in a chair for several brief periods. Sixty-four hours after admission, the blood chlorides were 428 mg., and the serum protein 6.7 gm. per 100 cc. Eighty-four hours after admission, there was clinical jaundice; the red-cell count was 4,900,000, with a hemoglobin of 104 per cent (16 gm.), the chlorides 425 mg. per 100 cc., the carbon dioxide combining power 56 vol. per cent, the serum van den Bergh (positive, direct) 23 units (115 mg. bilirubin per liter), and the serum protein 6.8 gm. per 100 cc. No clinical improvement was observed after the repeated use of Eschatin. The patient became increasingly stuporous, with a rising temperature and pulse. The urinary output was satisfactory throughout his course in the hospital. Death occurred 110 hours after admission.

Autopsy. The body was that of a well-developed and well-nourished young man. The burned areas showed a firm, dry tan without evidence of infection. All the tissues were moist and moderately icteric, and the body cavities contained a small quantity of bile-tinged fluid. The lungs were not remarkable except for slight edema and congestion. The heart, gastrointestinal tract, spleen, pancreas, adrenal glands and kidneys showed no gross anatomic changes. There was no ulceration of the duodenal mucosa. The liver weighed 1240 gm., and was soft and flabby. The cut surface revealed a finely mottled red-and-yellow appearance. There was dark thick concentrated bile in a small thin-walled gall bladder. The bile ducts were not remarkable and contained thin, clear bile.

Microscopic examination showed no histologic changes in any of the organs except the liver. There was extensive central hemorrhagic necrosis involving more than three quarters of the liver lobule, with disruption of the liver cords. Only a narrow zone of intact cells remained in the peripheral areas. These cells varied markedly in size and staining reaction. Many had large nuclei, with irregularly clumped chromatin. Mitotic figures were present, some of which were bizarre forms with scattered chromosomes. Definite evidence of regeneration was not demonstrated. Fat globules were present in slight degree through the area of necrosis and in the remaining liver cells. A moderate number of polymorphonuclear leukocytes infiltrated the interstitial tissue.

Comment. In this case, death was due solely to liver necrosis.

CASE 4. W. L. (H. H. 396,523), a 26-year-old man, was admitted on September 18, 1940. While the patient was working under his own car, a pan of gasoline caught fire and the flames spread to his clothing. He walked to the hospital. Diffuse burns involved the left side of the face, neck, chest, whole left upper extremity and the fingers of the right hand. The patient was put immediately in a tub of tannic acid solution and débrided. He remained in the tub 4½ hours. This treatment was followed by repeated spraying with tannic acid solution, which was immediately dried with a commercial hair drier. Intravenous glucose and two whole-blood transfusions were given. Fifteen hours after admission, the red-cell count was 5,060,000, with a hemoglobin of 97 per cent (15.0 gm.). Sixty-eight hours after admission, there was clinical jaundice, with an icteric index of 53. Ninety-one hours

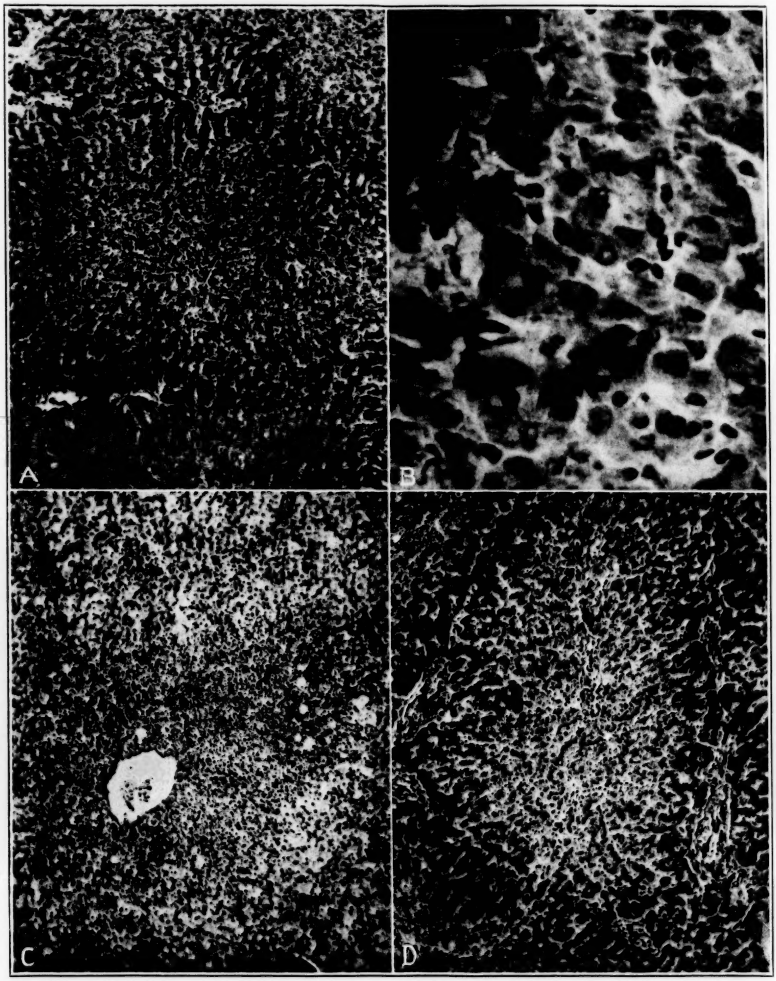

PLATE 1. *Human Liver Lesions Following the Administration of Tannic Acid for the Treatment of Burns.*

A. *Case 1. Early central necrosis (hematoxylin and eosin: × 100).*

B. *Case 1. Higher magnification of* A, *showing mitoses and other nuclear changes (hematoxylin and eosin: × 420).*

C. *Case 2. Advanced hemorrhagic central necrosis (hematoxylin and eosin: × 85).*

D. *Dr. Helpern's case. Intermediate central necrosis (hematoxylin and eosin: × 85).*

after admission, with a normal temperature but rising pulse, the nonprotein nitrogen was 80 mg. per 100 cc., the blood chloride 406 mg., the carbon dioxide combining power 54 vol. per cent, the serum protein 6.4 gm. per 100 cc., and the icteric index 100. The patient died 121 hours after admission.

Autopsy. The body was that of a well-nourished and well-developed young man presenting diffuse, satisfactorily tanned burns. There were slight generalized edema and moderate jaundice. The pericardial cavity was entirely obliterated by dense adhesions. The heart weighed 500 gm. Each pleural cavity contained about 200 cc. of bloody fluid. Each lung showed slight edema, and in the lateral portion of the left lower lobe, there was an area of pneumonic consolidation about 10 cm. in diameter. The peritoneal cavity contained 300 cc. of yellow fluid. There were hemorrhagic areas throughout the intestinal tract, but no ulceration. The liver weighed 2390 gm. There were multiple areas of subcapsular hemorrhage. The cut surface was a pale yellow brown, with small hemorrhagic areas throughout. The gall bladder and bile ducts were not remarkable.

On microscopic examination, the pulmonary areas of consolidation showed a characteristic pneumonic picture. The kidney tubules showed cloudy swelling. Almost the entire liver lobule was involved in hemorrhagic necrosis. Only in small foci in the periportal areas were intact cells present, and mitoses were infrequent. Slight diffuse leukocytic infiltration was present. Fat globules in moderate amount were noted in both necrotic and viable tissue. There was very little evidence of bile stasis.

Comment. The liver necrosis, which was the most massive of all the cases, was complicated by lobular pneumonia, inactive rheumatic heart disease and vascular failure.

Another case was brought to our attention by Dr. Milton Helpern, assistant medical examiner of New York City. A thirteen-month-old boy was severely scalded over the face, trunk and extremities. The local treatment was tannic acid and silver nitrate. The patient died eighty-two hours after the burn was sustained. The following description of the liver is quoted through the courtesy of the New York Hospital and the Department of Pathology, Cornell University Medical College (N. Y. H. 246,442, Necropsy 9780):

> *Gross.* The liver weighs 340 gm. The organ is of normal shape; it is firm but shows a moderate yellow discoloration. The central parts of the lobules are red.
>
> *Microscopic.* In the central half of the lobule, the liver cells are more pale-staining than in the peripheral half [Plate 1, *D*]. The nuclei of many liver cells are pyknotic, and some cells contain no nuclei. Some of the liver cells are eosinophilic. The liver cells in the peripheral half contain many fat vacuoles but are otherwise normal.

Until a few years ago, it could be truthfully stated that there are no internal or visceral lesions pathognomonic of burns and scalds.[4] Only recently has a specific histopathologic lesion in the liver been reported following certain severe burns. This lesion is so striking that, had it been present in earlier cases, it could not possibly have been overlooked by the army of clinical and experimental observers who have studied burns. In 1938, Wilson, Macgregor and Stewart[5] first described the appearance of the liver as follows:

> On naked eye examination, the liver was slightly enlarged, light yellow, soft, greasy and friable. On the cut surface, the lobular marking was conspicuous owing to greater pallor of the central zone; sometimes, however, haemorrhage in the central zones produced an appearance resembling "nutmeg" liver. On microscopic examination, necrosis of varying degree of the cells of the central parts of the lobules was seen. In the most extreme examples only a narrow strip of liver substance surrounding each portal tract showed surviving liver cells; the remainder were completely necrotic.

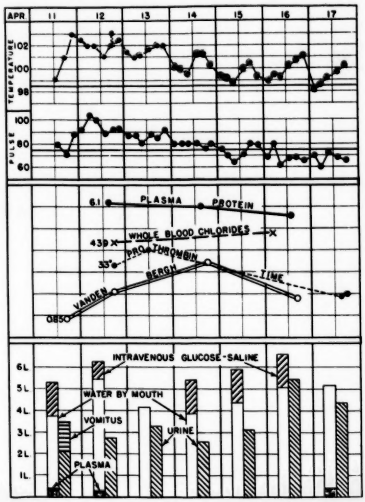

FIGURE 1. *Diagrammatic Summary of Data in Case 5.*

Similar cases at necropsy have been reported by Belt,[6] McClure,[7] Buis and Hartman[8] and others. This striking liver lesion has heretofore been attributed to toxemia or anoxia.

Furthermore, we have seen, and others have reported, human beings with burns treated with tannic acid who have shown definite clinical and chemical evidence of liver damage but have recovered. The following case is typical:

CASE 5. R. G. S. (H. H. 407,654), a 15-year-old boy, was stamping out a smouldering tree stump when it burst into flame and ignited his clothing. Burns involved both upper extremities, the left chest and axilla and the right lower extremity. Within 24 hours, there was evidence of liver damage, as indicated by the van den Bergh test and by the prothrombin time, which reached a maximum in 72 hours and then subsided (Fig. 1); the boy recovered, and was discharged from the hospital on the 18th day.

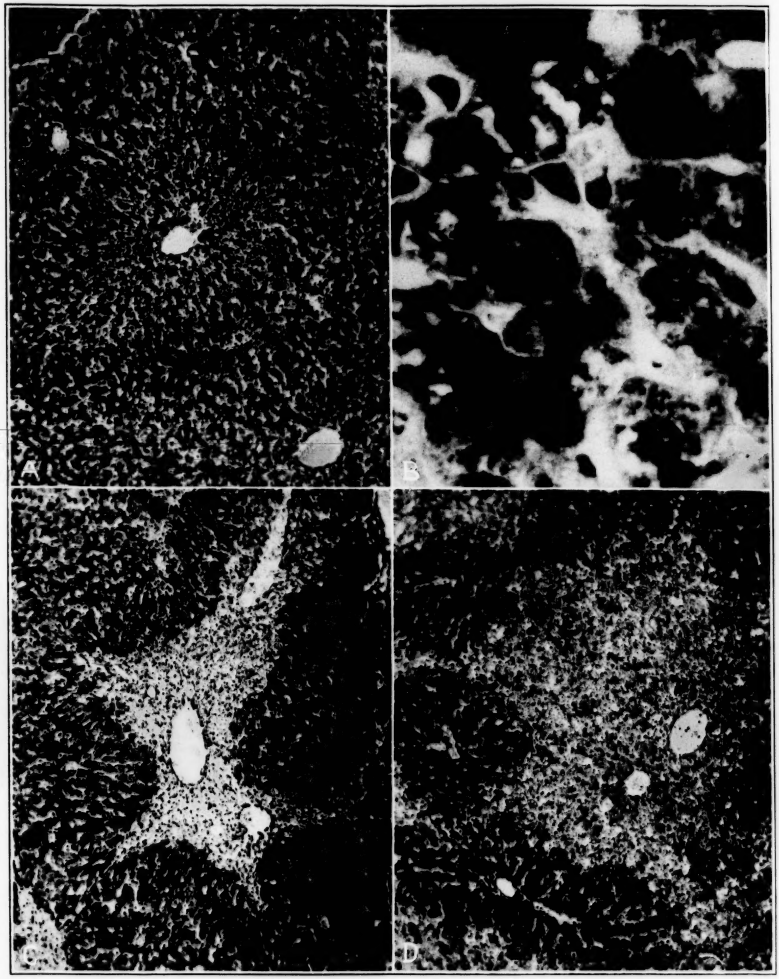

PLATE 2. *Experimental Liver Lesions in Rats Following the Administration of Tannic Acid.*

A. *Experiment 15 (Rat 6). Moderate central necrosis after 0.1 mg. tannic acid (hematoxylin and eosin: × 100).*

B. *Experiment 15 (Rat 6). Higher magnification of* A, *showing mitoses and other nuclear changes (hematoxylin and eosin: × 880).*

C. *Experiment 17 (Rat 4). Moderate central necrosis after 0.2 mg. tannic acid (hematoxylin and eosin: × 75).*

D. *Experiment 17 (Rat 1). Advanced central necrosis after 0.2 mg. tannic acid (hematoxylin and eosin: × 95).*

On review of the reported cases and particularly the proved cases coming to necropsy, the common denominator appeared to be that tannic acid had been employed in the treatment. Because it seemed to be of interest to investigate the possible role of tannic acid in the production of liver damage, a series of experiments was planned to determine the effect of subcutaneous injections of tannic acid on the liver in rats.

Albino rats weighing 70 to 90 gm. were selected. They were maintained on specified diets — one group on a house diet of raw bacon, lettuce, bread and grain, and the other on a standard diet of casein, sucrose, salts, cottonseed oil, cod-liver oil and brewers' yeast — for a week or more before being used, as well as throughout the period of experimental observation. Tannic acid (Mallinckrodt, *U.S.P.*, fluffy) was employed. Subcutaneous injections of a 5 or 10 per cent solution of tannic acid were given in doses that did not exceed 1.5 cc. at any one site, to avoid leakage and to facilitate absorption. No anesthesia was used. Rats that survived were killed on the third or fourth day by a blow on the head. The tissues were fixed by formalin or Zenker's fluid, and suitable sections were stained with hematoxylin and eosin.

The rats were injected, usually in groups of 6, with varying amounts (0.05 to 0.40 gm.) of tannic acid in from one to eight sites over a period of forty-eight hours (Table 1). Of the 77 rats injected, 8 failed to survive. Every one of the remainder showed some degree of liver damage, which, in general, varied directly with the amount of tannic acid injected and the number of injection sites employed. All other organs examined presented a normal appearance except for a slight cloudy swelling. No significant variation in the findings between the rats on either of the specified diets was observed.

The liver damage produced by these injections of tannic acid solution was characterized by: necrosis of the liver cells in the central portion of the lobule; a variable zone of intact cells in the peripheral area exhibiting a granular cytoplasm and enlargement of the nuclei, with irregular clumping of hyperchromatic nuclear material; regular and bizarre mitoses, some with dispersion of chromosomes, prominent in the liver cells at the periphery of the lobule; and hemorrhage and leukocytic infiltration, which were present in minor degree in areas of necrosis (Plate 2).

Attention should be called particularly to the fact that in these experiments the degree of liver damage varied directly with the total amount of tannic acid solution injected.

TABLE 1. *Summary of Rat Experiments.*

Experiment No.	No. of Rats	Dosage of Tannic Acid			Total Dosage	Rat Killed	Evidence of Liver Damage				Remarks
		Strength of Sol.	First Day	Second Day			Mitoses	Necrosis	Hemorrhage	Inflammation	
		%	cc. cc.	cc. cc.	gm.	day					
House Diet											
5	7	5	1.0		0.05	4th	±	±	0	0	
8	6	10	1.0		0.10	4th	±	+	0	0	
10	6	10	1.0 1.0		0.20	3rd	+	+ +	±	±	
12	6	10	1.0 1.0	1.0 1.0	0.40	3rd	+ +	+ + +	+ +	+	
Standard Diet											
15	6	5	1.0 1.0		0.10	3rd	+ + +	+ +	±	±	
16	6	5	1.0 1.0	1.0	0.15	3rd	+ +	+ + +	+	+	
17	6	5	1.0 1.0	1.0 1.0	0.20	3rd	+	+ + +	+	+	1 died within 24 hr.; another within 48 hr.
18	6	5	1.5 1.5		0.15	3rd	+	+ +	+	±	1 died within 48 hr.
19	6	5	1.5 1.5	1.5	0.23	3rd	+	+ + +	+	0	1 died within 24 hr.
20	6	5	1.5 1.5	1.5 1.5	0.30	3rd	+	+ + +	+ +	+	1 died within 48 hr.
21	6	5	1.0 1.0 1.0 1.0		0.20	3rd	+ +	+ +	+	+	
22	6	5	1.0 1.0 1.0 1.0	1.0 1.0	0.30	3rd	+	+ + +	+	+	1 died within 48 hr.
23	4	5	1.0 1.0 1.0 1.0	1.0 1.0 1.0 1.0	0.40	3rd	+	+ + +	+	±	1 died within 48 hr.

Discussion

The patients in the cases presented above died largely or solely as the result of a central liver necrosis. Such a necrosis has been observed, in our own cases and in those reported by others, only when the patient has been treated with tannic acid.

The sequence of possible lethal factors in burns treated with tannic acid is shown in Figure 2.

Other workers have burned experimental animals,[8] treated them with tannic acid jelly and produced a central liver necrosis comparable to that observed at autopsy in human beings who had

been treated with tannic acid. In our experiments, a series of rats was subcutaneously injected with chemically pure tannic acid and a central liver necrosis, comparable to that seen in the human patients, was produced. In these experiments, the degree of liver damage was in direct proportion to the amount of tannic acid injected subcutaneously. Similar results have been obtained after injection of rabbits and guinea pigs with tannic acid. No factor other than tannic acid has entered into the production of liver damage in these experiments.

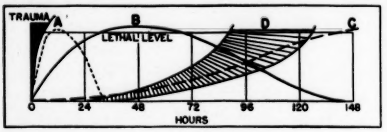

FIGURE 2. *Sequence of Lethal Factors in Burns Treated with Tannic Acid* (Adapted from Gunn and Hillsman[1]).

A. *Reflex shock from fright and pain.*

B. *Secondary shock or peripheral vascular failure due to increased capillary permeability and fluid loss or shift.*

C. *Bacterial contamination, which may become active infection in thirty-six to forty-eight hours.*

D. *Tannic acid poisoning, clinically demonstrable after thirty-six hours and fatal, owing to specific hepatitis, in ninety hours or more; the shift from vertical to horizontal crosshatching indicates the trend of increasing liver damage.*

CONCLUSIONS

In patients with severe burns treated with a tannic acid solution, tannic acid jelly or tannic acid and silver nitrate solutions, tannic acid poisoning resulting in a hepatitis may become clinically and chemically demonstrable within thirty-six hours and may result in death from a specific central necrosis of the liver in from eighty to one hundred and thirty hours or more.

The specific central necrosis of the liver due to tannic acid poisoning should be distinguished from the cause or causes of the so-called "toxemias" of burns and scalds.

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DISCUSSION

DR. W. IRVING CLARK (Worcester, Massachusetts): I doubt if many of us here have followed the effect of tannic acid treatment in cases of fatal burns through to the conclusion of examination of the liver.

To me, the whole matter is extremely new, and I probably have not been following the literature, although I believe, from talking to Dr. Wells; that the literature is not very profuse on this subject.

It is interesting to follow the exact course of argument in this paper. In the first place, the statement is made definitely that there has been no pathological examination showing necrosis of the liver in cases of burns prior to the use of tannic acid; secondly, this is corroborated by finding necrosis of the liver in the cases presented; thirdly, animal experimentation has been carried out in which animals have been burned, subjected to tannic acid treatment and, then, autopsied, with the finding of central liver necrosis; and fourthly, animal experimentation by tannic acid alone has presented liver necrosis.

The cause of this necrosis is unknown. There has been much discussion about toxemia, which has generally been accepted by most authors. One finds in the literature that the toxemia of burns is a recognized condition, but whether it is due to histamine or to some other substance has never been definitely proved.

The interesting points that I should like to bring out are that chloroform produces a somewhat similar picture, and that inhalation of the fumes of chlorinated hydrocarbons causes a very similar necrosis.

In each of these cases, chloroform and the chlorinated hydrocarbons, one finds that the greater the amount of chlorine in the formula, the more definite and more acute the necrosis. For example, with carbon tetrachloride, a long exposure and a considerable amount of fume must be present before necrosis occurs, whereas with the more complicated chlorinated hydrocarbons such as the "pentas" and "hexas," the condition occurs with comparatively slight exposure.

Those two drugs may perhaps give a suggestion of the cause of this central necrosis. It does not seem logical that tannic acid itself should produce it; possibly, it does, but the question is whether the tannic acid may not produce in the body a change in the metabolism in some way by which there is hyperchlorinization of the tissues. I think that this is a purely speculative matter, which should be discussed by pathologists in the future; this may be a step toward the solution of the problem.

The question that I suppose we are all asking ourselves is this, Do these experiments suggest that tannic acid as a treatment of burns should be omitted and some other form of treatment employed?

DR. WELLS (closing): The question that one immediately asks is, If tannic acid produces a specific and often fatal hepatitis, should it be abandoned as a local dressing in severe diffuse burns?

The employment of tannic acid is still, in my opinion, the best treatment for the local injury, and I am not quite ready to abandon it. It may result in the death of certain patients who have been burned, but, frankly, I know of no better local dressing at the present time. Operations for cancer of the stomach may result in the death of certain patients, since the mortality from the operation of subtotal or total gastrectomy is not negligible. However, gastric resection is at present the best treatment for carcinoma of the stomach, and in the hope of saving a patient doomed to die unless the growth can be totally extirpated, both patient and surgeon must accept the risk. A consideration of the mortality in more than 700 burns

treated at the Hartford Hospital during the last twenty-five years shows that since tannic acid was introduced the gross mortality has been cut in half. This is not by any means entirely due to the employment of tannic acid—I am sure of that. Many factors have entered into the improvement of the records, but I am satisfied that tannic acid has helped to reduce the morbidity and mortality of burns.

PRESIDENTIAL ADDRESS*

JAMES B. WOODMAN, M.D.†

FRANKLIN, NEW HAMPSHIRE

MY father, who was a physician in a small town in central New Hampshire, once told me that, when the way seemed dark and I might be blamed for what was not my fault, I should remember that there would also be times when I would be praised and honored more than I deserved.

The latter part of this admonition comes to my mind in the present situation. And I consequently wish to express my heartfelt appreciation for the high honor of being the president of this society, and to tell you that I have for the past year been inwardly basking in the warming sunshine of your favor.

This evening, it seems not inappropriate to present to you briefly four of the names that have made New Hampshire medical history, and the history of the Dartmouth Medical School, noteworthy.

In presenting Drs. Twitchell, Mussey, Crosby and Peaslee, may I remind you that the whole state of New Hampshire contains fewer souls than the city of Boston alone, and that in the period of which I speak we were largely a farming population, widely scattered, with no hospitals and no centers, in the modern sense, for medical research? There were no modern laboratories, no electricity, no trains, no automobiles, no telephones, no good roads and, worst of all, no asepsis and, until near the end of the period, no anesthetics. Can you not see these gentlemen starting out for a distant village or farm, in their clothes of a former generation, on horseback, or in their two-wheeled chaises, toiling over the sandy, snow-bound or muddy roads? And before them and after them, one generation after another, struggling toward the light.

These four great men and great surgeons, country doctors and pioneers of their line, were all New Hampshire men. They were educated at Dartmouth College. They worked and taught at the Dartmouth Medical School. They passed on the knowledge they acquired to future generations. They were all a part of the New Hampshire medical tradition of which we are so proud.

Amos Twitchell was born in Dublin on April 11, 1781, on the slopes of old Mt. Monadnock, and it was said of him that he was as grand and honest as the old mountain itself. He possessed initiative, and was of the type of pioneer surgeons who have done so much the world over to make our present-day work possible. He was a poor farm boy, entirely lacking in this world's goods but blessed with an ambition that is a greater endowment. He prepared for college at New Ipswich Academy, entered Dartmouth at the age of seventeen, received his degree in 1802, and immediately began the study of medicine under Dr. Nathan Smith. He became a very proficient anatomist and in due time became assistant to Dr. Smith and was thus associated with him for some time at the medical school. He then practiced for short periods in Norwich, Vermont, and Marlboro, New Hampshire.

While in Marlboro, he encountered the case that brought him prominence at the time, and fame ever since. In October, 1807, John Taggart, of Sharon, had been shot in the neck while attending some military maneuvers. His jaw was shattered, all adjacent parts were severely bruised, and extensive mortification had set in. On the tenth day, while dressing the wound, Dr. Twitchell remarked that the common carotid artery was bare and appeared to be sloughed on its surface. While he was leaving the house, a terrific hemorrhage started, the blood spurting, as he says in his account of the case, a distance of three or four feet. He swiftly removed the dressings and placed his thumb over the bleeding point, and with only the help of the boy's mother, he cut down on the artery and finally succeeded in working around it by blunt dissection and getting a ligature on it. This was followed by some oozing, and as soon as pressure was removed, by some spurting. The lad was by this time unconscious and his condition was precarious, so that no further attempt at ligation was attempted. The bleeding point was then compressed by a small piece of dry sponge,

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†Member of staff, Franklin Hospital, Franklin, New Hampshire.

covered by larger pieces to a depth of two or three inches, and this inverted cone was held down by bandages about the head and neck for pressure. The patient recovered. This operation was original, so far as Dr. Twitchell was concerned: although it had been performed by Fleming, an English surgeon, in 1803, it was not reported until 1817.

Dr. Twitchell did all the major operations of the day, and did them repeatedly. In one year, he performed three tracheotomies for the removal of foreign bodies, and all were successful. Can you visualize him doing this emergency operation on a small infant's short, fat neck and without an anesthetic? He frequently operated for stone in the bladder. In 1838, he removed the arm, scapula and part of the clavicle for an enormous osteoma; this was the third time such an operation had been done, each previous one having been performed by a New Hampshire surgeon. He trephined the tibia for abscess, did excisions of the joints and had performed ovariotomies before it was known that McDowell had done the operation.

Dr. Twitchell was a fine Christian, a genial gentleman and a tireless worker; he was extremely temperate and inclined to be a vegetarian. He was three times president of the New Hampshire Medical Society and always took an active part in the meetings, giving much attention to the eradication of quacks and charlatans, with which the state seemed to be afflicted at this time.

He was offered professorships at Dartmouth Medical School, Castleton and Vermont University but was unable to accept, partly from financial considerations and partly on account of his health. In his correspondence, I find a letter to the president of Dartmouth College in which he expressed the hope that the stipend might be raised to $1200 per annum, that he might not be obliged to sustain too great a financial loss.

Reuben Dimond Mussey was born in Pelham on June 23, 1780. He was the son of Dr. John Mussey, who bore a good reputation as a physician in his locality. There was not much money available in the family, but after district school he managed to attend the academy at Amherst. He was then obliged to earn enough for his further education by working on a farm and teaching school. His father had been able to teach him Latin, which was a prerequisite in those days. He must have worked to good advantage, for at the age of twenty-one he entered the junior class at Dartmouth College. He continued to teach during vacations, and he graduated from college in 1803 and immediately became a pupil of Dr. Nathan Smith. At the end of this course, he sustained a public examination, and read and defended a thesis on dysentery; the degree of B.M. was conferred on him in 1805. In 1812, he received his M.D. from the University of Pennsylvania School of Medicine. He was then called back to Hanover, where he was a professor in the medical college from 1814 to 1838. He then taught at Bowdoin for four years; later, he was professor of surgery at the University of Cincinnati College of Medicine for fourteen years and at Miami Medical College, which he founded, for five years.

As a surgeon, he enjoyed a reputation second to none in the state:

> So-called brilliant surgery he regarded with contempt. He cared not to make a figure but to benefit his patient; not to gain eclat, but to save human life. He believed much in skilled surgery, something in Nature, but most of all in God. Frequently on the eve of a great operation he knelt at the bedside and sought skill and strength and success from the great source of all vitality.

Doubtless, the confidence and sense of peace following this must have been of great advantage to both surgeon and patient at the operation. I think you will all agree with me that we have a dread of operating on one who lacks this confidence.

Mussey's famous discussion with Sir Astley Cooper over the healing of intracapsular fractures is well known and gave him, at the time, much prominence, since it was somewhat unusual, as he remarked, to win an argument with "one who was always positive, and sometimes right."

Dr. Mussey is said to have been very skillful with his hands and to have handled the knife precisely and cleanly, a quality conducive to good healing in his day as in ours. Evidence of his dexterity is a clock still in the possession of his descendants; he made this when a young man. While in college, he also made his own shoes.

The case that brought him the greatest fame was probably that in which he successfully ligated both carotid arteries. He did this operation for Mr. Jason Pettee, a resident of Hanover, and the operation was performed for a bleeding nevus of the vertex of the head, which threatened a speedy death. He tied one carotid, and twelve days later he tied the other. A few weeks later, he successfully removed the tumor. This was the first recorded case in which both carotids were successfully tied. Naturally enough, the operation gave him a reputation all over the surgical world.

He removed a boy's tongue, which measured eight inches in circumference and projected five inches beyond the jaws, and the patient recovered. At one operation, he removed the scapula and a large part of the clavicle from a patient for whom he had previously amputated at the shoulder joint. Dr. Mussey mistakenly supposed that this

was the first operation of the kind in the history of surgery. As a matter of fact, it was first done by Dr. Dixi Crosby in 1836, and then by Dr. Mussey in 1837 and by Dr. Twitchell in 1838—all New Hampshire surgeons. Dr. Mussey several times removed the upper and portions of the lower jaw. His records show that he did lithotomies in 49 cases; all but 4 patients recovered. He repaired strangulated hernias in 40 cases, with only 8 deaths. He treated 45 cases of varicocele successfully. He operated for perineal fistula in 4 cases and for impermeable stricture of the urethra in 2, and did a large number of plastic operations, with fine results. He also successfully treated a rectovaginal fistula. These are only a few samples of the enormous amount of work he was constantly carrying on.

Dr. Mussey was a small man with a high forehead, high cheek bones, a thin face and square chin. He had a brusque, rather forbidding manner. His Puritan ancestry gave him none of the sparkle that we now speak of as personality. He won his reputation purely on merit. His motto was, "Do well and wait." As a young man, he was dyspeptic and developed the habit of living on a strictly vegetable diet, and this rule was followed more or less all his life. He was a very religious man and very abstemious. Many of his speeches and pamphlets were directed against the use of alcohol and tobacco. At one time during his later life, his physician prescribed some stimulant. He finally consented to take some brandy in eight-drop doses, from which he said he could feel quite a strong effect. In those days, when liquor was so universally and so freely used, he must have felt that he had won his argument for temperance, for in spite of his dyspepsia he lived to the ripe age of eighty-six.

Dr. Mussey's sons, grandsons, great-grandsons and so on, without a break in the line, were physicians down to the seventh generation, which is represented, I am informed, at the present time by a young man who is a student at Dartmouth Medical School.

Dixi Crosby was born at Sandwich on February 9, 1800, shortly after his father, Dr. Asa Crosby, had been ordered out of Moultonboro by the sheriff for fear that he might become a financial burden on the town, on account of his poor health. Dr. Asa had ten sons, several of whom became physicians. Prior to Dixi's birth, there naturally had been much speculation about whether this child, too, would be a boy. Dr. Asa had favored another son, and when the youngster arrived on the scene and it was ascertained that it was a boy, the exulting father exclaimed "*Dixi*," or "I told you so." And Dixi he remained.

Up to his nineteenth year, young Crosby had not been much interested in books and had made an early venture into business. This however, was not a success, and he finally returned home to Gilmanton, where the family then resided. He studied with his father, a method of gaining knowledge and experience prevalent in those days, and one that, it seems to me, has much to recommend it. He also attended Gilmanton Academy and later went to Dartmouth College. He was a keen student of anatomy, and one of his biographers has a good deal to say regarding certain difficulties in which he found himself over the procuring of anatomic material, which at that time was extremely difficult to obtain.

After receiving his degree from Dartmouth Medical School, he practiced for ten years in Gilmanton and for three years in Laconia, then known as Meredith Bridge. He had by that time established a fine reputation as a surgeon, and in 1838 he was called to take the chair of surgery and obstetrics at Dartmouth by Dr. Mussey, who was retiring. He held this position for thirty-two years.

His brother, Nathan, in his book, *A Crosby Family*, tells of Dixi's first major operation. It was done while Dixi was in his first year of medical study. He accompanied his father to a consultation in the case of a man whose leg had been frozen, and whose condition was most critical. It was agreed by the physicians that amputation at an earlier stage might have saved the patient's life, but that it was now too late to attempt it. Young Crosby urged that the operation still be performed. The elders shook their heads. He even proposed to attempt it himself, but this was met with a storm of disapproval. During the night, the patient was being attended by young Crosby, and the following conversation is quoted. "Look here, young man, did you ever cut off a leg?" "No sir, but I should like to." "Will you cut off mine?" "Yes, if you will let me." "Well, young man, if I live till morning you shall cut off my leg, and I will take the chances." In the morning, all the elders joined in protest against the operation, and Dixi's father said, "Don't do it, Dixi, you can't succeed and if the man dies they will kill you." But the patient was firm, and the student was ready. The leg was removed, and the man recovered.

During the following year, father and son were called in while at a distant village to see a man who had just had a severe accident to his leg, demanding amputation. The father was for giving it up, since he did not have his instruments with him. The more resourceful young Crosby sharpened a carving knife, filed a saw and did the amputation, which was successful.

These early incidents are pointers to his later teachings to his pupils. He often said to them,

"Depend on yourselves, young gentlemen; take no man's diagnosis, but see with your own eyes, feel with your own fingers, judge with your own judgment and be the disciple of no man."

Dr. Crosby, although a surgeon by nature and by preference, was in no modern sense, a specialist. His professional and professorial labors included obstetrics as well as surgery, and his practice was enormous. Probably no man ever did more surgery in the State than he, and his surgical diocese extended from Lake Champlain to Boston.

Dr. Crosby was the first to devise the method of reduction of dislocations of the phalanges by flexion, some of which had previously been irreducible. He was the first to open abscess of the hip joint. Most of his operations were done before he had ever seen them done by anyone. He was not a rapid or spectacular operator. His motto was that an operation was soon enough done when it was well enough done.

His brother speaks of him as follows:

> [He was] a handsome, brilliant, cheery, chatty man. He could sing, tell a good story, was kindly and civil, had agreeable manners, had cultivated the proprieties of social life, and had entered upon a religious life, a combination forming ballast to stand any amount of sail or storm, any success or discouragement.

Dixi Crosby passed his declining years in Hanover and passed on his mantle to his distinguished son and inseparable companion, Dr. Alpheus Benning Crosby, affectionately known as "Dr. Ben."

Edmund Randolph Peaslee was born in Newton on January 22, 1814. He was educated at New Hampton and Atkinson academies and at Dartmouth College and Dartmouth Medical School, from which institution he graduated in 1838. He also received his M.D. degree from Yale. Following this, he studied extensively in Europe. He was then recalled to Dartmouth and appointed lecturer in anatomy and physiology. He taught at Dartmouth for twenty-seven years. He also taught at Bowdoin, at New York University College of Medicine and at Bellevue. He received an LL.D. from Yale University, as well as Dartmouth. He was a great scholar and a great gentleman. His greatest work was done in the field of gynecology, and his writings on gynecologic subjects were prolific and scholarly. He was the first to remove both ovaries through a single incision. He was also the first to use vaginal drainage after a laparotomy. He was the first to flush out the abdominal cavity after laparotomy.

One of his friends described him as a tall, spare man, with a long beard, which early became snow white. In appearance, he was said to be as fragile and as cold as an icicle from his own native land. Oliver Wendell Holmes, who was his contemporary on the faculty of Dartmouth Medical School, said, "He looked as if his circulating capital might consist of a hundred or two red globules, with twice as many white ones, in a half a pint of serum, yet he outlived scores of prize-fighters." His appearance must have been deceptive, for he did an enormous amount of work for many years and was ever ready for more.

He was a most sympathetic and helpful friend and adviser of his students, all of whom he regarded and spoke of as "my boys."

He, too, was a fine Christian gentleman, with whom duty was the ruling passion. His contemporaries expressed their esteem for his character and scholarly attainments by making him president of the New Hampshire Medical Society, of the New York Academy of Medicine, of the Medical Society of the County of New York, of the New York Obstetrical Society, of the New York Pathological Society and of the American Gynecological Society; at the time of his death, he was a trustee of Dartmouth College and of the New York Academy of Medicine, corresponding fellow of the Obstetrical Society of Berlin and honorary fellow of the obstetric societies of London, Boston and Louisville.

* * *

These, in brief, are the lives of four great seekers for the light. Their careers suggest to me that oft-quoted passage:

> Happy is the man that findeth wisdom, and the man that getteth understanding. For the merchandise of it is better than the merchandise of silver, and the gain thereof than fine gold. She is more precious than rubies: and all the things thou canst desire are not to be compared unto her. Length of days is in her right hand; and in her left hand riches and honour. Her ways are ways of pleasantness, and all her paths are peace.
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> *Proverbs* 3:13–17.

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CLINICAL ASPECTS OF PAROXYSMAL RAPID HEART ACTION*

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NUMEROUS publications bearing on the occurrence, mechanism and treatment of the various paroxysmal tachycardias are available. Analysis of the clinical manifestations of paroxysmal rapid heart action has not, however, received the attention it deserves. These data are essential to a complete understanding of the clinical problems created by these arrhythmias under different circumstances, of their prognosis and, to some extent, of their treatment. This study was made in an attempt to provide such data.

MATERIAL

Data were obtained in 125 cases. Electrocardiograms were made during the paroxysm in every case but 1, and during normal rhythm in most. Ventricular rates were obtained from the electrocardiograms. There were 81 cases (65 per cent) of paroxysmal auricular fibrillation, 24 (20 per cent) of paroxysmal auricular tachycardia, 11 (8 per cent) of paroxysmal auricular flutter and 9 (7 per cent) of paroxysmal ventricular tachycardia. The types of heart disease‡ represented were: valvular heart disease (including 2 cases of subacute bacterial endocarditis), 25 cases (18 per cent) — 16 of these patients had mitral stenosis, 5 had aortic valvular disease without other valvular involvement, and 4 had mitral stenosis and aortic valvular disease (in 1 case, combined with tricuspid stenosis); angina pectoris of effort, 20 cases (14 per cent); acute or recent cardiac infarction, 24 cases (17 per cent); chronic arterial hypertension, with or without definite evidence of heart involvement (cases with concomitant valvular or coronary-artery disease are not included in this group), 23 cases (17 per cent); coronary-artery disease without angina of effort or acute or recent cardiac infarction, 10 cases (7 per cent) — the term "asymptomatic coronary disease" was applied to this group; hyperthyroidism, 8 cases (6 per cent); normal hearts, including 4 cases of hyperthyroidism, 25 cases (18 per cent); miscellaneous types, comprising 1 case each of acute simple fibrinous pericarditis, chronic cor pulmonale and acute cor pulmonale, 3 cases (2 per cent). Among these cases, there were 19 patients with congestive failure and 2 with cardiac asthma.

The type of patient, ventricular rate, cardiac lesion, functional status of the circulation and the occurrence of palpitation, pulmonary congestion, angina pectoris (or status anginosus), circulatory collapse, congestive failure, various cerebral phenomena and embolism were analyzed, to determine what correlations existed. The available data in some cases were inadequate for clinical analysis; these cases, in addition to the others, were utilized to determine the influence of digitalis on the ventricular rate in paroxysmal auricular fibrillation.

ASYMPTOMATIC CASES

Symptoms were not provoked by paroxysms of rapid heart action in 41 cases, almost one third of the entire series. The ages of the patients ranged from two to eighty years. This group included 5 cases (12 per cent) of paroxysmal auricular tachycardia, 28 (68 per cent) of paroxysmal auricular fibrillation, 5 (12 per cent) of paroxysmal auricular flutter and 3 (7 per cent) of paroxysmal ventricular tachycardia. The incidence of the various arrhythmias in this group is no different from that of the entire series.

Thirteen patients (32 per cent) had normal hearts, including 3 with hyperthyroidism (7 per cent); 10 (24 per cent) had hypertension with or without definite evidence of heart involvement (1 of these had hyperthyroidism); 10 (24 per cent) had acute or recent cardiac infarction; 4 (10 per cent) had asymptomatic coronary-artery disease; 2 (5 per cent) had rheumatic heart disease, and 1 had acute fibrinous pericarditis, 1 chronic cor pulmonale, 1 acute cor pulmonale and 1 angina pectoris. There was 1 case of congestive failure. The incidence of thyrotoxicosis, hypertension, acute or recent myocardial infarction and asymptomatic coronary disease is the same in this group as in the entire series of 125 cases, whereas the incidence of normal hearts is higher, and that of valvular disease, angina pectoris and congestive failure much lower than in the series as a whole. Embolism occurred in 4 cases. Extracardiac factors, which may possibly have had some bearing on the occurrence of the arrhythmia, were present in each case with a normal heart¶: namely, anesthesia and

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‡Classified according to etiology, the 125 cases accounted for 138 listings, this discrepancy being occasioned by the inclusion of some cases of coronary-artery disease in three different groups — asymptomatic, angina of effort and acute cardiac infarction — when observations were available during paroxysms of rapid heart action in more than one of these clinical states.

¶There are, of course, many examples of paroxysmal rapid heart action in patients with normal hearts in whom obvious or apparent exciting causes are not evident.

surgery, hyperthyroidism, acute mediastinitis, bronchopneumonia, gangrenous appendicitis and subacute yellow atrophy of the liver.

The ventricular rates ranged from 80 to 250, but were 150 or less in 18 (44 per cent) and more than 170 in 8 (19 per cent) of the cases. Of the 18 patients with rates of 150 or less, the paroxysm of rapid heart action occurred postoperatively in 3, following hemiplegia in 1, and during the course of bronchopneumonia in 2. On the other hand, of the remaining 23 cases with rates exceeding 150, 9 were postoperative; 1 patient had subacute bacterial endocarditis, 1 had gangrenous appendicitis, 1 had acute rheumatic fever, and 1 had bronchopneumonia. Seven of the 8 cases in which the rate exceeded 170 were postoperative. Only 11 cases were not postoperative or did not have extracardiac disease, and in 10 of these the ventricular rate was less than 170; none of these patients had normal hearts. In 3 of the cases with embolism, the ventricular rate was 140 or less.

Cases with Palpitation

Palpitation was the sole symptom provoked by paroxysmal rapid heart action in 17 cases. The ages of the patients ranged from twenty-one to sixty-one years. Of these, there were 3 cases (18 per cent) of paroxysmal auricular tachycardia, 13 (76 per cent) of paroxysmal auricular fibrillation, and 1 (6 per cent) of paroxysmal auricular flutter. The incidence of the various arrhythmias in this group differs from that of the entire series of 125 cases only in the absence of ventricular tachycardia. Eight patients (47 per cent) had normal hearts, 4 (24 per cent) had hypertension, 4 (24 per cent) had rheumatic heart disease, and 2 (12 per cent) had angina pectoris—1 with rheumatic heart disease. The occurrence of hypertension, rheumatic heart disease and angina pectoris was the same in this group as in the entire series of 125 cases, whereas the incidence of acute or recent myocardial infarction was much less and, in normal hearts, much greater than in the entire series. There was no case of congestive failure or embolism.

The ventricular rate was 150 per minute, or less, in 11 (65 per cent) of the cases, and more than 170 in only 1 case. In contrast to the group without symptoms, there were no postoperative cases, and the only extracardiac conditions were a lung tumor and carbon monoxide poisoning. Moreover, 4 patients were described as "nervous," and 1 was having menopausal symptoms. Of the 8 patients with normal hearts, 3 were nervous, 1 had a lung tumor, and 1 had carbon monoxide poisoning. The ventricular rates in the 2 cases of angina pectoris were 124 and 140, respectively, and in the 4 cases of rheumatic heart disease 124, 160 to 180, 140, and 110 to 130, respectively.

Cases with Pulmonary Congestion

Dyspnea, wheezing, pulmonary edema and hemoptysis may be provoked by paroxysmal rapid heart action. After exclusion of cases of congestive failure and angina pectoris, there remain 11 in which one or more of these symptoms were observed during paroxysms of rapid heart action.

Mitral stenosis was present in 10 cases, and hyperthyroidism in 1. The paroxysm of rapid heart action in the latter occurred during an acute illness characterized by fever, marked but temporary dilatation of the heart and pericardial and pleural friction rubs; following subsidence of the acute condition and control of the hyperthyroidism by thyroidectomy, numerous paroxysms of auricular fibrillation, during a period of eleven years, failed to provoke dyspnea. There were 9 cases of auricular fibrillation, and 2 of auricular flutter. The slowest ventricular rate, 140 per minute, was observed in 2 cases, whereas in the rest, the rate was 150 or more. Embolism complicated the arrhythmia in 4 cases. The ages ranged from nineteen to fifty-five years.

However, not all patients with mitral stenosis exhibit manifestations of pulmonary congestion during paroxysms of rapid heart action. It was not present in 4 cases. In 3, the ventricular rates were 124, 140, and 110 to 130, respectively, and in only 1 was the rate greater than 150 (160 to 180).

Cases of Angina and Coronary-Artery Disease

Angina pectoris was induced by paroxysmal rapid heart action in 15 cases. The ages in this group ranged from forty-four to seventy-five years. There were 4 cases (27 per cent) of paroxysmal auricular tachycardia, 10 (67 per cent) of paroxysmal auricular fibrillation, and 1 (6 per cent) of paroxysmal ventricular tachycardia. It is clear that the incidence of the various arrhythmias in this group is not significantly different from that in the entire series of 125 cases. The ventricular rate was 150 per minute or more in 12 cases, 140 in 2, and 120 in 1. Embolism complicated the arrhythmia in 2 patients with paroxysmal auricular fibrillation. There were 2 cases of mitral stenosis, with evidence of coronary-artery disease in 1, and 1 case of hyperthyroidism in which a routine post-mortem examination showed normal coronary arteries. Hypertension was present in 5 cases. Twelve patients gave a clear history of angina on effort, but no such history was obtained in 3 cases. In one case, paroxysms of auricular tachycardia recurred for thirty-six years without induc-

ing anginal pain; finally, however, although angina of effort had never yet been experienced, a paroxysm provoked pain. A short time after this episode, cardiac infarction occurred, and following recovery from the acute condition, angina was induced both by effort and by paroxysmal rapid heart action. Another case was similar, in that angina was induced by paroxysms of rapid heart action, but not by effort; it differed in one important aspect, however: cardiac infarction did not supervene, despite the lapse of considerable time. This patient was elderly and crippled by arthritis. The first attack of paroxysmal auricular fibrillation in still another case provoked angina pectoris, which had never been produced by effort. However, shortly following this event, there was an attack of cardiac infarction, uncomplicated by any disturbance of the heart rhythm. During convalescence, a paroxysm of auricular fibrillation failed to produce any symptoms but palpitation. In none of these cases was the variation in response to paroxysmal rapid heart action ascribable to a change in the ventricular rate.

In contrast to these 15 cases are 3 in which paroxysmal rapid heart action failed to induce angina pectoris, although effort did provoke this syndrome. The ventricular rates were 124, 140 to 145, and 140 per minute, respectively.

In 8 cases with significant coronary-artery disease but without a history of angina on effort or acute or recent cardiac infarction, it is noteworthy that paroxysmal rapid heart action did not induce angina pectoris. In 6 cases, the ventricular rates were quite rapid, being 215, 175, 166, 190, 200 and 150 per minute, respectively. Significant coronary-artery disease was revealed by post-mortem examination in 4 cases, and by a history of old cardiac infarction antedating the occurrence of paroxysmal ventricular tachycardia in the other 2. The 2 remaining cases of asymptomatic coronary-artery disease had ventricular rates of 120, and 120 to 140, respectively.

Twenty-four cases of acute and recent cardiac infarction were complicated by paroxysmal rapid heart action — 3 (13 per cent) by paroxysmal auricular tachycardia, 13 (54 per cent) by paroxysmal auricular fibrillation, 4 (17 per cent) by paroxysmal auricular flutter, and 4 (17 per cent) by paroxysmal ventricular tachycardia. The incidence of auricular flutter and ventricular tachycardia was higher than in the entire series of 125 cases, but otherwise there was no difference between this group and the entire series. The occurrence of paroxysmal tachycardia is unusual before the third day following the onset of cardiac infarction, the greatest incidence coming on or after the fifth day. Thus, of 18 cases studied adequately, 14 exhibited paroxysmal rapid heart action three days to two months following acute cardiac infarction; in no case was anginal pain induced, even though the ventricular rate was 150 per minute, or more, in all but 3. None of these patients experienced anginal pain spontaneously or as the result of effort. In 1 case, angina of effort continued after an episode of myocardial infarction and was also induced by paroxysmal ventricular tachycardia at a rate of 187. In 3 cases, paroxysmal rapid heart action and cardiac infarction appeared to have a simultaneous onset. In 1 case, paroxysmal auricular tachycardia and cardiac infarction occurred simultaneously, and, as so often happens under these circumstances, the precise sequence of events remains uncertain; the significant fact is the continuance of the paroxysmal tachycardia for twenty-four hours following the cessation of pain. Four and a half hours after a similar onset in another case, the paroxysmal tachycardia ended, but pain and shock continued for three or four days. Prior to the onset of the attack in these 2 cases, angina on effort had never been experienced, and four years prior to the attack in the latter case, paroxysmal auricular tachycardia with a rate of 200 failed to induce angina pectoris. The third case was similar to these in that paroxysmal auricular fibrillation apparently induced angina pectoris in a patient who had never experienced such pain on effort, and the obvious fact soon emerged that cardiac infarction was in progress. The possibility that paroxysmal rapid heart action precipitated acute coronary thrombosis or cardiac infarction in these 3 cases must be considered. It has been suggested[1] that paroxysmal rapid heart action, by further impairing an already abnormal coronary circulation, may predispose to or precipitate acute coronary thrombosis or cardiac infarction; convincing evidence is difficult to obtain, but 2 cases in addition to those just described are suggestive. In these, pain occurred some hours after cessation of a paroxysmal arrhythmia; myocardial infarction was found at autopsy in both.

Cases of Congestive Failure

Congestive failure was present in 19 cases, in 15 of which it was possible to estimate the effect of paroxysmal rapid heart action on the degree of failure. There were 6 cases (40 per cent) of paroxysmal auricular tachycardia, 5 (33 per cent) of paroxysmal auricular fibrillation, 2 (13 per cent) of paroxysmal auricular flutter, and 2 (13 per cent) of paroxysmal ventricular tachycardia. The ages ranged from thirty-four to sixty-eight years. Rheumatic valvular disease (including 1 case of subacute bacterial endocarditis) was present in 7 cases

(47 per cent), hypertension without additional etiologic factors in 4 (27 per cent), and coronary-artery disease in four (27 per cent). The ventricular rate was 150 per minute or more in 10 cases, 140 in 3, and 130 and 120, respectively, in 2. Embolism occurred in 1 case of paroxysmal auricular tachycardia and in 2 cases of paroxysmal auricular fibrillation, and in 1 case of mitral stenosis complicated by paroxysmal auricular flutter, autopsy revealed old splenic infarcts and terminal coronary thrombosis.

In 14 cases, there was noted, as a result of the paroxysms of rapid heart action, an increased severity of such manifestations as dyspnea, orthopnea, congested liver and edema, and a drop in the urinary output, or renal failure, coma and death; in some of these cases, there was a prompt and striking clinical improvement following the resumption of normal rhythm. Gross congestive failure was evident prior to the onset of tachycardia in all but 1 case, in which, however, chronic hypertension, cardiac enlargement and exertional dyspnea indicated the probability of incipient failure or poor cardiac reserve. Evidence of gross failure first appeared, and then rapidly progressed, at the end of ten days of paroxysmal auricular tachycardia with a ventricular rate of 210 per minute; rapid improvement followed resumption of normal rhythm. In an additional case, in which the ventricular rate was 120 per minute, the arrhythmia appeared to have no obvious influence on the functional status of the cardiovascular system.

Cases with Central-Nervous-System Manifestations

Irrationality, confusion, psychosis, coma and convulsions may be observed during attacks of paroxysmal tachycardia. Six patients exhibited one or more of these manifestations. The ages ranged from sixty-one to seventy-one years. There were 2 cases of paroxysmal auricular tachycardia, 2 of paroxysmal auricular fibrillation, and 2 of paroxysmal ventricular tachycardia. Four patients had hypertension, and 2 had coronary-artery disease. There were 3 cases of congestive failure, 1 of cerebral embolism, 1 of pulmonary embolism, and 1 of pulmonary thrombosis. The ventricular rates were 150 to 200 per minute.

One patient was "euphoric and queer" before the onset of paroxysmal ventricular tachycardia, which precipitated an acute psychosis. In another, irrationality, which had been previously noted, was increased during a paroxysm of auricular tachycardia. Another patient showed signs of mental confusion accompanying an attack of auricular fibrillation, which was complicated by cerebral embolism. Paroxysmal auricular tachycardia in a case of congestive failure brought about renal failure, which was followed by coma. Unconsciousness occurred as a transitory phenomenon at the onset of paroxysmal ventricular tachycardia in a patient with a ventricular rate of 190, whereas in another, unconsciousness and convulsions occurred at the end of a paroxysm of auricular fibrillation, presumably from cardiac standstill before the re-establishment of a normal sinus mechanism. In the last case, there were no heart sounds during the seizure, but unfortunately it was not possible to obtain an electrocardiogram during the period of apparent cardiac standstill.

Cases with Vascular Collapse

Although a fall in blood pressure was commonly observed during paroxysmal rapid heart action, in only 15 cases did collapse occur. The ages ranged from thirteen to sixty-eight years. There were 5 cases (33 per cent) each of paroxysmal auricular tachycardia and paroxysmal auricular fibrillation, 3 (20 per cent) of paroxysmal auricular flutter, and 2 (14 per cent) of paroxysmal ventricular tachycardia. Four patients had normal hearts (1 with hyperthyroidism), 5 had mitral stenosis, 1 had free aortic insufficiency, 2 had angina pectoris, 2 had asymptomatic coronary-artery disease, and 1 had recent cardiac infarction. Only 1 case of hypertension (in a patient with mitral stenosis) occurred in this group. Four patients had congestive failure. Embolism complicated the arrhythmia in 5 cases. The ventricular rate was 200 per minute or more in 7, or almost half the cases, and was less than 150 in only 2.

Cases of Embolism

Embolism complicated the paroxysmal arrhythmia in 18 cases; pulmonary-artery thrombosis occurred in 1 case. The ages ranged from nineteen to sixty-eight years. All types of arrhythmia were represented: 2 cases (11 per cent) of paroxysmal auricular tachycardia, 11 (58 per cent) of paroxysmal auricular fibrillation, 3 (16 per cent) of paroxysmal auricular flutter, and 3 (16 per cent) of paroxysmal ventricular tachycardia. Mitral stenosis was present in 7 cases, coronary-artery disease in 7, hypertension in 4 (with mitral stenosis in 1), and a normal heart in 1. Four patients were in congestive failure. Pulmonary embolism occurred in 16 cases, but the diagnosis was doubtful in 2; cerebral, renal, splenic and axial embolisms were also observed. The ventricular rates ranged from 120 to 220 per minute. Embolism preceded, and probably provoked, the arrhythmia in 3 cases, and was followed by vascular collapse in 7. Dyspnea occurred in only 5 cases, and hemoptysis in 2, all being cases of mitral stenosis;

pulmonary edema occurred in 1 case of mitral stenosis. In 2 cases, the advent of embolism appeared to provoke no symptoms; the ventricular rate was 120 and 140 respectively, in these.

Effect of Digitalis

Digitalis was being taken by 29 patients prior to the onset of a paroxysm of auricular fibrillation in which observations could be made. The ventricular rates in these cases were compared with those in 52 patients who did not receive digitalis. The paroxysms observed numbered 30 and 55, respectively; the ventricular rate was less than 140 in 14 (47 per cent) and more than 140 in 16 (53 per cent) of the paroxysms in the former group, and less than 140 in 11 (20 per cent) and more than 140 in 44 (80 per cent) in the latter group. In 6 cases, observations of the ventricular rate were made in paroxysms of auricular fibrillation both before and after the administration of digitalis. The ventricular rate was significantly lower after digitalization in 4 of these and was unchanged in 2. The ventricular rate in 16 fully digitalized cases was less than 140 in 7, and 140 or more in 9; in 7 cases that were overdigitalized (excessive amounts of the drug, or digitalis intoxication), the ventricular rate was less than 140 in 4, and 140 or more in 3; in 2 partially digitalized cases, the rates were 140 and 130, respectively; in 4 cases, the amount of digitalis taken was unknown.

Among the 15 digitalized cases in which the ventricular rate was 140 or more, normal hearts were present in 4, acute cardiac infarction in 1, hyperthyroidism in 1, and congestive failure in 3; in the last 3 cases, the ventricular rates were the slowest of this group — 140, 140 and 150, respectively. The group of 14 with ventricular rates under 140 contained no patients with normal hearts, 2 with hyperthyroidism (1 of whom received iodine in addition to digitalis), 2 with acute cardiac infarction, and 5 with congestive failure.

Digitalis administered between paroxysms of auricular fibrillation is effective in controlling the ventricular rate during the paroxysm in some, but not in all, cases. The ventricular rate was significantly slow in 20 per cent of patients who had not had any digitalis, a fact that should be considered in appraising the above data; moreover, in 2 cases in which digitalis appeared to be effective, other factors were operative — one patient, with hyperthyroidism, received iodine in addition to digitalis, and the other had a 2:1 auriculoventricular block. It is obvious that in more than half the patients digitalis did not prevent ventricular rates that were rapid enough to induce symptoms, even when excessive amounts of the drug were used. Digitalis is least effective in those with normal hearts, and displays its greatest influence on the ventricular rate in patients with congestive heart failure.

Since it is not my purpose to provide an elaborate presentation of treatment, the consideration of the effect of digitalis and other therapeutic agents on the other arrhythmias is omitted.

Discussion

Correlation of certain symptom groups with the ventricular rate, type of patient, cardiac lesion and presence or absence of embolism and congestive failure (Table 1) reveals that most of the symptoms are provoked under definite conditions and relations, and there is thus created, within broad limits, a fixed and uniform clinical pattern. The remaining symptoms, which are not susceptible to such correlation, must be differentiated from the cardinal manifestations of paroxysmal tachycardia and regarded as minor or noncharacteristic; some of these are nausea, vomiting, weakness, dizziness, precordial pain or aching, sweating, feeling of warmth, faintness, apprehension, nervousness, polyuria, fever and leukocytosis; a slight to moderate drop in blood pressure is very common, and rarely, in cases of congestive failure, the blood pressure may rise. Following a paroxysm of auricular tachycardia pain, tenderness and swelling of the left shoulder, accompanied by fever, leukocytosis and rapid sedimentation rate, were observed in 1 patient; these manifestations rapidly subsided.

The ventricular rate and, to a lesser extent, the type of arrhythmia are significant in determining symptoms. Symptoms are not often provoked by rates under 150 per minute, which may be regarded as the critical level, unless embolism complicates the paroxysm. With extremely rapid ventricular rates, on the other hand, symptoms are almost always induced, regardless of the type of heart lesion and even if the heart is normal. When symptoms fail to appear during paroxysms with rates somewhat above the critical level, the explanation is usually to be found in the type of patient, who is "insensitive" naturally or as the result of grave illness, or has been rendered so by heavy sedation. The group in which palpitation occurs as the only symptom differs most strikingly from the asymptomatic one in relation to the type of patient; "sensitiveness" is common, and conditions requiring heavy sedation are absent. The lack of symptoms other than palpitation is to be explained on the basis of the ventricular rate.

A comparison of the ventricular rates in the different types of rapid heart action is of some interest. The slowest rate (excluding cases of auricular fibrillation), 124, occurred in paroxysmal auricular tachycardia; the fastest rate, 260, in a case of auricular flutter with 1:1 ventricular response. The ventricular rate in auricular fibrillation is usually under 170, and only rarely 200 or more. The

fastest rates occur in auricular flutter during periods of 1:1 response. In paroxysmal auricular tachycardia, the ventricular rate, as a rule, does not exceed 220. Excessively rapid ventricular rates, in the vicinity of 300, were not observed in the present series, but many cases are on record. These are usually, probably always, examples of auricular flutter with 1:1 ventricular response.[2-21] Two cases of auricular flutter with 1:1 ventricular response occurred in this series, and may be added to those already reported.[22, 23]

The significance of the type of rhythm is seen in auricular fibrillation and paroxysmal ventricular tachycardia. Embolism is much more frequent in the former than in all the other types of arrhythmia, and whereas the immediate consequences of paroxysmal ventricular tachycardia are no different from those in the other arrhythmias under identical conditions, the mortality is highest in this group, probably on account of the seriousness of the underlying heart condition, or the conversion of the paroxysmal ventricular tachycardia into ventricular fibrillation.

The influence of the heart lesion and of the functional status of the circulation on the type of clinical response to paroxysmal rapid heart action is decisive, and may be best observed in cases of mitral stenosis, angina pectoris of effort and congestive heart failure. The characteristic response in cases of compensated mitral stenosis consists of dyspnea, orthopnea, asthma, pulmonary edema and hemoptysis. These manifestations usually occur when the ventricular rate is 150 per minute or more; pulmonary congestion is not induced when the ventricular rate is well under this level, but is rarely absent when it is exceeded. These clinical phenomena, in some cases, may be less pronounced when, in addition to mitral stenosis, there is aortic valvular disease, congestive failure or vascular collapse. The clinical and x-ray manifestations of the pulmonary congestion disappear with remarkable rapidity when normal rhythm is resumed. A spontaneous diuresis may then be observed, even though there is a complete absence of manifest edema or other fluid accumulations (except in the lungs). The extent of the response, or the lack of it, depends not only on the ventricular rate but also on the degree of mitral stenosis.

In compensated valvular heart disease other than mitral stenosis, regardless of the ventricular rate, pulmonary congestion is not induced.

In cases of congestive failure and angina pectoris, as well as in cases of mitral stenosis, dyspnea may be one of the consequences of paroxysmal rapid heart action. When it occurs in angina pectoris, it accompanies anginal pain, which is the

TABLE 1. *Correlation of Clinical Data.*

SYMPTOM OR COMPLICATION	HEART LESION	VENTRICULAR RATE	TYPE OF PATIENT	EMBOLISM
Asymptomatic	None, or any type	Usually, 150 per minute or less	"Insensitive"	Uncommon
Palpitation	None, or any type	Usually, 150 per minute or less	"Sensitive"	Never
Pulmonary congestion	Mitral stenosis	Usually, 150 per minute or more		Common
Angina pectoris	Angina pectoris of effort; occasionally, aortic valvular disease.	Usually, 150 per minute or more		Uncommon
Central-nervous-system manifestations				
Loss of consciousness, with or without convulsions	None, or any type	Usually, 200 per minute or more (cardiac standstill)		May occur (not essential)
		Rate unimportant		Always (cerebral)
Mental confusion or acute psychosis	None, or any type; hypertensive and coronary disease and congestive failure common.	Rate unimportant if cerebral embolism occurs; otherwise, usually, 150 per minute or more.	Functional nervous disorders or organic cerebral disease	May be causative (not essential)
Coma	Congestive failure, renal failure.	Usually, 150 per minute or more		May be causative (not essential)
Congestive failure	Any type (pre-existing congestive failure or very poor reserve)	Usually, 150 per minute or more		Common
Vascular collapse	None, or any type	Usually, 200 per minute (less in elderly patients)		May occur (not essential)
	Aortic valvular disease	Rate unimportant		May occur (not essential)
	None, or any type	Rate unimportant		Always
Embolism	None, or any type (mitral stenosis commonest)		Commonest with auricular fibrillation; may occur with auricular flutter or paroxysmal tachycardia.	

leading symptom induced by the tachycardia, and is no different from the dyspnea experienced in attacks of angina that occur spontaneously or are provoked by effort. Similarly, in congestive failure, dyspnea, like the other manifestations of myocardial insufficiency, — congested liver, edema and so forth, — is increased in severity but is evident before the onset of the tachycardia.

Paroxysmal rapid heart action increases the severity of pre-existing congestive failure and may precipitate gross congestive failure in cases with limited cardiac reserve if the paroxysm is unduly prolonged or the ventricular rate is extremely rapid. When the paroxysms are transitory or the ventricular rates are considerably below 150 per minute, no effect on congestive failure is observed. The essential factor in this group of cases is not the type of heart lesion, but the functional status of the cardiovascular system. Embolism does not occur so preponderantly in cases of paroxysmal auricular fibrillation and of mitral stenosis when congestive failure is present as when it is absent. When symptoms are stated in publications concerning paroxysmal tachycardia, dyspnea or other manifestations of congestive failure are usually given a prominent place. Perusal of individual case reports often reveals the existence of mitral stenosis, congestive failure and angina pectoris. This coincides with my own findings, and these cases will not be reviewed here. There are, however, many case reports in which these conditions are not reported to be present, even though the clinical data are fully recorded, but in which dyspnea or other manifestations of congestive failure first appear after the onset of paroxysmal rapid heart action.[2, 4, 7–9, 12, 14, 16, 18, 19, 21, 24–26]

The cases referred to are selected as examples of dyspnea or congestive failure brought on by paroxysmal rapid heart action in patients who, prior to the onset of tachycardia, presumably had normal hearts; these furnish a striking contrast to the cases reported in this paper and indicate the need for careful observation of additional clinical material before the relation of dyspnea and failure to various factors can be fully expressed. From the recorded case histories, however, certain conclusions appear to be justified. There is a preponderance, in this group, of infants and young children. In most cases, the ventricular rates were extremely rapid, attaining or approaching the highest rates known to occur; in many, the paroxysms were unusually long. Infection preceding the onset of tachycardia was commonly observed, and was followed by clinical evidence of acute myocardial disease in some and by post-mortem demonstration of diffuse myocarditis in others. In some of the recorded cases, conditions besides cardiac disease have been responsible for the occurrence of dyspnea. Finally, in most patients with extremely rapid heart rates, auricular flutter is responsible for the tachycardia; the extreme rate is due to a paroxysm of 1:1 ventricular response in the course of an established flutter.[22]

Patients who experience angina pectoris on effort invariably suffer similar attacks during paroxysms of rapid heart action, provided that the ventricular rate is 150 or more per minute; pain is never provoked if the rate is well under 150, unless digitalis has been taken. It is noteworthy that in cases of extensive coronary disease without angina pectoris, paroxysmal tachycardia, even with extremely rapid rates, does not induce anginal pain. Only occasionally does paroxysmal rapid heart action induce anginal pain in those who have never experienced angina on effort. This is true in elderly crippled patients whose activity is seriously hampered and, rarely, in those with aortic insufficiency; it may constitute a premonitory warning that acute cardiac infarction is soon to occur or is already in progress. Under the latter two conditions, the possibility that the paroxysm of rapid heart action has precipitated acute coronary thrombosis or cardiac infarction must be considered. Paroxysmal rapid heart action complicating acute cardiac infarction does not materially influence the pain, which may cease even though the tachycardia continues unabated.

When one appraises an attack of paroxysmal rapid heart action accompanied by angina pectoris (or status anginosus), two possibilities must be considered: the attack may represent the induction of angina by paroxysmal rapid heart action, or acute coronary thrombosis or cardiac infarction may have taken place. If the history reveals the past occurrence of angina on effort, it is probable that the former situation prevails, notwithstanding the presence of fever, leukocytosis and even embolism; the pain, fever and leukocytosis (if there is no embolism) promptly disappear on cessation of the tachycardia. On the other hand, if angina on effort has never occurred, serious consideration must be given to the diagnosis of acute cardiac infarction. If the pain continues after normal rhythm has been resumed, if the pain disappears while the tachycardia remains in progress without a significant lowering of the ventricular rate, if there is vascular collapse despite a moderate ventricular rate, and if the temperature and white-cell count do not rapidly revert to normal levels on cessation of the tachycardia, it is highly probable that acute cardiac infarction has occurred. Rarely, paroxysmal rapid heart action may begin after the onset of angina pectoris, of which it is then a complication.[27]

The significance of the cardiac lesion is illustrated in those patients who have had paroxysmal tachycardia for a long time — in some cases twenty-five to fifty years. Repeated attacks may fail to induce symptoms until, years after the onset of paroxysmal rapid heart action, significant coronary-artery disease and angina of effort develop, with consequent induction of angina during paroxysms of tachycardia.

Three factors appear to be significant in the genesis of vascular collapse: extremely rapid ventricular rates, embolism and aortic valvular disease. Extremely rapid ventricular rates and embolism occur in half and one third of the cases, respectively. When extremely rapid ventricular rates are attained, all other factors may be absent, and the heart may be normal. If embolism complicates the tachycardia, the ventricular rate and the type of cardiac lesion are not significant. In the presence of aortic valvular disease, vascular collapse may occur, even though the ventricular rate is significantly under 150 per minute and embolism is absent. Although the 2 patients with slow ventricular rates were in congestive failure, it is unlikely that the latter is essential in the production of vascular collapse when the ventricular rate is slow; one patient had aortic valvular disease, and the other case was complicated by embolism. The age factor appears to be largely unimportant. Occasionally, in elderly patients, vascular collapse may occur with only moderately rapid ventricular rates, even though other contributing factors are not evident.

Cerebral manifestations are not uncommon. The age range in this group is higher than in the other groups, and the incidence of hypertension, congestive failure, embolism (or arterial thrombosis) and functional or organic cerebral disease is high. The events witnessed in this group are associated with various circumstances, which may be summarized as follows. Unconsciousness, with or without convulsions, may be provoked by a single factor, — extremely rapid ventricular rates or transitory cardiac standstill, — and may be seen in healthy young adults with normal hearts. When cerebral embolism complicates paroxysmal rapid heart action, loss of consciousness and convulsions or other cerebral manifestations may occur, regardless of the ventricular rate. In patients with functional nervous disorders or organic cerebral disease, paroxysmal arrhythmias with ventricular rates usually greater than 150 per minute may provoke confusion, irrationality or acute psychosis. It may therefore be stated that the induction of central-nervous-system manifestations depends on three factors: the ventricular rate, the "type" of patient and the organic cerebral disease. The type of heart lesion is not important, since patients with normal hearts, as well as those with various types of heart disease, are seen in this group; the high incidence of hypertension and coronary-artery disease is probably explained by the frequency with which functional and organic cerebral disorders accompany these conditions. The best examples of cerebral manifestations are probably seen in cases with unusually rapid ventricular rates, as in auricular flutter with 1:1 ventricular response, when the rates approach 300.[4, 8, 10, 11, 16, 17, 22, 26–32] On the other hand, even with extremely rapid ventricular rates, cerebral or other manifestations may be singularly absent.[2, 6, 13] Under cerebral manifestations, Barnes[30] includes vertigo, hemianopsia, temporary blindness, fainting, falling, with or without loss of consciousness, and epileptiform seizures.

Embolism may complicate any type of paroxysmal rapid heart action, occurring in patients of any age and with any type of heart disease. It is commonest in the presence of mitral stenosis and with auricular fibrillation. The most frequent consequences are circulatory collapse and dyspnea, the latter, in this series, occurring only in cases of mitral stenosis. The most frequent site of embolism is the lungs. Although embolism complicates the arrhythmia in most cases, the former may precede and provoke the latter; this sequence occurred in 1 case of auricular fibrillation and in 2 of auricular flutter.

Paroxysmal rapid heart action may cause death as the result of heart failure, vascular collapse, embolism, renal failure, the conversion of the paroxysmal arrhythmia into ventricular fibrillation, or cardiac standstill.

Paroxysmal auricular tachycardia may occur in patients who at other times exhibit carotid-sinus sensitivity. Nevertheless, pressure exerted over the carotid sinus may not influence the paroxysm. In some cases, this failure of response may be associated with a marked fall in blood pressure, which accompanies the tachycardia, whereas in others the same phenomenon is observed even though a drop in blood pressure has not occurred.

The four types of paroxysmal rapid heart action with which this report is concerned were associated with many different extracardiac conditions, especially in the patients with normal hearts: gastrointestinal disturbances (including peptic ulcer, gall-bladder disease, carcinoma, acute gangrenous appendicitis and incarcerated hernia), anesthesia, surgery, infections (pneumonia, peritonitis, pericarditis, acute mediastinitis, pulmonary tuberculosis, chronic pulmonary infections, pyelitis, wound sepsis, furunculosis and acute tonsillitis), lung tumor, embolism, trauma, carbon monoxide poisoning, exertion (including such activities as turning or twisting of the body, laughing and sneezing), emotional

upsets, hyperthyroidism, menopausal disturbances, acute yellow atrophy of the liver and the use of digitalis. The relation of many of these conditions to the inception of auricular fibrillation is discussed, and the literature reviewed, by Parkinson and Campbell.[27]

There is considerable experimental and clinical evidence that digitalis may provoke or prolong paroxysms of auricular fibrillation.[17, 27, 33–39] For this reason alone, one may doubt the advisability of routine digitalis therapy in such cases. Furthermore, the ventricular rate is not always rapidly controlled, and it is of greater fundamental value to abolish the abnormal rhythm. Digitalis is not indicated in paroxysms of auricular fibrillation when the ventricular rate is less than 150 per minute, and in any event, regardless of the rate, if symptoms are not provoked by the paroxysm. The wisdom of continually using digitalis for the avowed purpose of assuring a slow ventricular rate whenever a paroxysm of auricular fibrillation occurs may be seriously questioned on the basis of the evidence. In a considerable number of cases, under these circumstances, a ventricular rate sufficiently slow to prevent the development of symptoms is not achieved.

Summary

The clinical data of 125 cases of paroxysmal rapid heart action are analyzed.

The cardinal symptoms and signs are correlated with certain significant variables in the individual patient. It has been shown that the various phenomena occurring in paroxysmal rapid heart action arise under definite conditions and relations and thus create, within broad limits, a uniform clinical pattern.

The cardinal manifestations of paroxysmal rapid heart action are palpitation, pulmonary congestion (dyspnea, wheezing, pulmonary edema and hemoptysis), angina pectoris or status anginosus, congestive failure, vascular collapse, cerebral manifestations and embolism. In many cases, no symptoms are provoked.

The significant variables are the type of patient, the heart lesion, the functional status of the circulation, the ventricular rate (and in a lesser degree the type of rhythm) and the presence or absence of embolism.

The most characteristic responses occur in cases of mitral stenosis, angina pectoris and congestive failure.

The critical level of the ventricular rate is approximately 150 per minute. As a rule, manifestations are not provoked below this level. The characteristic consequences of extreme rates are discussed.

The effect of digitalis on the ventricular rate in cases of paroxysmal auricular fibrillation is discussed.

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THE CHEMICAL MEASUREMENT AND CONTROL OF CLINICAL VITAMIN DEFICIENCY*

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THE past decade has contributed not only a more detailed description of clinical deficiency disease, including several syndromes and symptoms hitherto unrecognized in man,[1] but also significant advances in the knowledge of the chemical nature of these interesting accessory food substances. In general, gross vitamin deficiencies continue to be diagnosed through the aid of the five senses, in addition to common sense. Nevertheless, the use of objective tests is desirable for three purposes: to confirm clinical diagnosis and so maintain a high standard of accuracy therein; to serve as a court of appeal in doubtful cases, particularly in the region of partial vitamin collapse that Minot[2] has termed the "twilight zone of vitamin deficiency"; and to check the effectiveness of therapy. The need for the first of these objectives is obvious. The need for the last two is becoming clearer as physiologic studies are demonstrating that vague apathies and lack of efficiency are produced by incipient vitamin lack, which causes symptoms commonly known as "subclinical." For example, for many years it has been known that a patient with pellagra may show no *pelle agra* until exposure to actinic rays is used to bring out the peculiarity of the condition.

In the field of neuropsychiatry, in particular, the lack of vitamin B complex is becoming more and more important. Thus, Jolliffe and his associates[3] have demonstrated that on a thiamin-deficient diet healthy interns in a hospital underwent a considerable loss of "energy" and even showed changes in personality within a relatively few days. Indeed, many patients in severe illness are subject to a lack of vitamin intake not unlike that which these experimental observations produced, and it remains to be seen to what extent severe or debilitating disease produces a similar change in personality through lack of these essential substances. In the intricate fields of neurasthenia and psychoneurosis, this problem may also complicate the picture. For this reason, there is a wide opportunity for the use of chemical methods in the investigation of routine patients, even those whose symptomatology is not very dramatic. Such determinations, of course, should not replace careful dietary histories or painstaking physical diagnosis. They should be used in a confirmatory sense.

With the development of knowledge concerning the nature of the vitamins have come appropriate chemical methods for their determination. These chemical procedures are far more practical and convenient than the older mammalian assays, which are so costly and time-consuming that for clinical purposes they are not practical. To be sure, they may still be used occasionally to check the chemical methods employed for clinical purposes. Likewise, in recent years, the use of microorganisms for biologic assay has extended the practicability of the biologic method for testing vitamin concentration. For example, in the assay of biotin, the vitamin universally needed for growth, it is possible to measure extraordinarily small amounts of material. One makes the measurement by studying the effects on the growth of microorganisms of amounts of this substance that are of the order of a small fraction of a millionth of a gram. If, however, practical application in clinical cases is to be hoped for, it will probably come chiefly through the use of chemical tests.

Two main difficulties have stood in the way of the development of such reactions. The first is that such extraordinarily minute amounts of the material are needed in nature; this follows from the fact that the vitamins in general are to be thought of as natural catalysts. Indeed, some of them are known to contribute the precise prosthetic groups that determine the specificity of enzymes. In this respect, they are analogous to the haptophore groups that Ehrlich postulated for antibodies. The second difficulty is that, obviously, to detect such small amounts of material by a practical chemical procedure, one often has to sacrifice a certain degree of specificity. Therefore, so far as chemical specificity has been sacrificed, the method is subject to error. In spite of these difficulties, tests are already available that can be used in clinical cases; they are simple enough to be performed in any large clinic that has in operation research laboratories for routine clinical studies.

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*This article comprises a seminar held by the Department of Pharmacology, Yale University School of Medicine, on January 26, 1942. Among the various members contributing, I am especially indebted to my colleague, Professor George R. Cowgill, and to my associate, Dr. Rigby C. Roskelley.

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Several of the vitamins have been discovered so recently that as yet their detection is largely a biologic affair. Accordingly, it is not practical to expect their analysis in clinical cases for some time. Of the better known vitamins, however, simple chemical methods have now been developed for carotene and vitamin A, for thiamin, for riboflavin, for ascorbic acid and for nicotinic acid. Fortunately, it is becoming progressively clearer that vitamin deficiency, as it is encountered clinically, is usually multiple. Accordingly, in many cases, if one detects the lack of one of these well-known vitamins and thus confirms the noncommittal diagnosis of "vitamin deficiency," there are likely to be deficiencies of other vitamins not specifically tested. For this reason, the administration of the one pure vitamin recognized as lacking in a given case may remedy only part of the patient's difficulty. If, however, a well-balanced diet is included in the therapeutic regimen, natural foodstuffs will probably correct any serious deficiency of some of the less well-known vitamins. More experience is needed in this field, but it is already clear, for example, that in clinical pellagra there is a deficiency, usually of nicotinic acid, but frequently also of thiamin or riboflavin. Indeed, these secondary deficiencies account for the wide differences in symptomatology and in response to therapy of individual cases.

Technical Possibilities

In general, two main procedures are available for detecting vitamin deficiency chemically — the first, through the determination of the concentration of vitamin in the blood, and the second, through the study of urinary excretion. At one time, it was thought that a low vitamin concentration in the blood strongly indicated a vitamin deficiency. This is now known not necessarily to be so. For example, the investigations of Mindlin and Butler[4] have shown that the vitamin C content of the plasma may undergo considerable fluctuations for a short time in fairly normal subjects, and that the plasma level may drop to very low concentrations while the tissue reservoirs of vitamin are still entirely adequate. It may be said, therefore, that whereas a high vitamin level in the blood ordinarily rules out deficiency of the antiscorbutic vitamin, a low level does not necessarily mean that the patient's tissues are really suffering from its lack. Furthermore, with the other vitamins, a normal blood concentration may exist in the presence of undoubted deficiency, as will be explained presently.

In such cases, the study of urinary secretion is of more value. To be sure, collection of urine involves extra work, and is subject to the errors of decomposition and loss. Nevertheless, if one finds that a patient is still excreting considerable amounts of vitamin in the urine, one is assured that there is an excess of that vitamin in the organism. On the contrary, if the vitamin excretion is low, one may assume that no such excess of the essential factor exists. Furthermore, urinary studies may be extended by the use of the so-called "vitamin-tolerance test." In this technic, a known amount of vitamin is administered, and its fate by urinary excretion is subsequently determined. If the tissues have been hungry for vitamins, they will retain a large portion of the vitamin administered. If, on the other hand, the tissues have already been replete with vitamin stores, they will fail to retain so considerable a portion of the vitamin administered.

In such a test, if the vitamin is administered orally, one must take special precautions to exclude conditions that would interfere with the absorption of the vitamin by the alimentary tract. The same precautions hold for subcutaneous administration in edematous patients. On the other hand, it is not always desirable to administer vitamins by vein. For example, even in vitamin-deficient persons, if thiamin is administered intravenously, a large amount may run out through the kidneys before the tissues have a sufficient opportunity to affix the thiamin. It will be apparent that it is easier technically to rule out vitamin deficiency than to verify it, and that whenever such a test reveals vitamin deficiency, the technic must be scrutinized carefully and the test repeated, to exclude, so far as possible, technical errors such as those discussed.

Analytical Methods

So far as the chemical procedures now available are concerned, it must be remarked at the outset that there are frequently two or more competing methods for the determination of a given vitamin. In certain cases, one must weigh the expense of a complicated apparatus like a spectrophotometer against excessive labor costs or fatigue when a more tedious procedure is used. In other cases, a test requiring a considerable degree of skillful technical manipulation may have to be abandoned in favor of a simpler but more costly one. For this reason, the choice of the methods mentioned below is at best arbitrary, but in my opinion and that of my associates, they offer the best compromise between the various factors described.

Whatever method is chosen, it is always well to repeat the determination in cases suggesting vitamin deficiency before administering therapy, and to repeat the test at various intervals after the therapy is begun. This is especially desirable in cases in which the so-called "conditioned vitamin deficiency" is suspected. This sort of de-

ficiency, which occurs when the dietary history is apparently adequate, has been described by Strauss,[5] Richardson[6] and Salter.[7] It is particularly common, as Castle et al.[8] have pointed out, in conditions involving the gastrointestinal tract. In these cases, owing to failure of absorption, the tissues suffer from vitamin lack although the diet contains an adequate amount of vitamin. If, in such circumstances, chemical responses in blood or urine can be recognized when the vitamin is administered, and especially if clinical improvement occurs simultaneously, the chance of error can be greatly reduced.

One further complication that may be encountered is the problem of the provitamin, of which carotene is a classical example with reference to vitamin A. Moore[9] and others have shown that crystalline carotene, although not in itself a vitamin, relieves vitamin A deficiencies and causes vitamin A to increase in concentration in the body fluids and in tissues like the liver. In the analysis of foodstuffs, therefore, the content of provitamin may be more significant than that of the vitamin itself. Nevertheless, in the body fluids or tissues, the vitamin is ordinarily the important form in relation to deficiency disease.

Vitamin A

Although the existence of vitamin A has been known for many years and its relation to carotene studied carefully, practical methods for the quantitative determination of this vitamin in human blood are only in a preliminary stage. The detection of vitamin A deficiency by the use of biophotometers for night blindness, or hemeralopia, has had a vogue in recent years, but it has become apparent that this method is fraught with many complications. Accordingly, investigators are turning back to the direct measurement of vitamin A in serum or plasma to determine a deficiency of this vitamin. In general, the tests are based on two optical procedures: the colorimetric and the spectrometric.

The first of these utilizes the classic Price–Carr blue reaction, which the vitamin gives with antimony trichloride under certain conditions. The difficulty is that this color is evanescent and is not altogether specific for vitamin A. Some of the difficulties involved have been summarized by Lindqvist.[10] Because of these obstacles, Munsell[11] thinks that the spectrometric method of analysis holds more promise. Nevertheless, by the use of the photoelectric colorimeter or a step-photometer, it has been possible already to analyze the plasma or serum of the blood under different conditions. The results are apparently consistent within themselves, although there is a considerable difficulty in any investigation in converting the values given back into absolute terms.

Accordingly, at present, many clinical values are merely stated in "blue units" to indicate that the conversion factor of these units in actual concentrations is a matter of conjecture. Nevertheless, as reported by Pett and LePage,[12] within four hours after the ingestion of 20,000 international units of vitamin A, the plasma "blue unit" value rose from 76 to 133 international units. The rise indicated that about 10 per cent of the vitamin administered was in the circulation. The authors found that 88.0 microgm. of beta-carotene gave the same blue color as 84.1 international units of vitamin A. Accordingly, some method of correction must be made for the carotene test. The carotene, however, can be determined by other methods, the simplest of which makes use of the characteristic yellow color of this substance.

In his comprehensive monograph on the absorption, metabolism and storage of vitamin A and carotene, With[13] has discussed the behavior of these absorptive bands toward ultraviolet light from the standpoint of routine analytical procedures. He emphasizes the great variation in the conversion factors found by independent investigators. The same author has also collected many valuable data on the metabolism of these two related substances. He points out that normal subjects most frequently show a serum carotenoid concentration of between 20 and 50 microgm. per 100 cc. Values over 100 microgm. are rare. In the blood from the umbilical cord, however, values of about 10 microgm. are ordinarily found. The carotene content of serum, expressed as percentage of the total carotenoid, is highly variable. It ranges from one tenth to one half of the total.

Only rarely does vitamin A pass through the kidney into the urine. Pregnancy may be an exception; likewise, the urine may contain vitamin A in cases of infectious disease, liver lesions, malignant tumors and diabetic acidosis. In such cases, perhaps, it is combined with abnormal excretory substances.

Tolerance tests give, as they are applied at present, no information about the carotenoid or vitamin content of the organism.

The photometric technic has been applied in a number of interesting clinical conditions. For example, May and McCreary[14] have used a photelometric method reported by Dann and Evelyn[15] to determine the vitamin A content of serum in celiac disease. Clausen and McCoord,[16] using a similar method, found that the mean vitamin A was 20.2 *U.S.P.* units per 100 cc. of plasma; the standard deviation was 10 units. Pett and LePage[12] obtained values in relatively normal subjects ranging from 50 to 90 international units per 100 cc. of plasma. These data showed a good correlation with visual tests. In natives of Batavia suffering

from xerophthalmia, deHaas and Meulemans[17] observed no more than a trace of vitamin A in the serum. Similarly, Clausen and McCoord[16] found that infection caused a prompt fall in the concentration of carotene and vitamin A in the plasma. Similar studies have been made by Wilbur[18] in adults and by May, Blackfan, McCreary and Allen[19] in children.

Somewhat paradoxical results have been found in diseases that involve disturbances of lipoid metabolism. For example, in hypothyroidism, the content of the plasma may be low in vitamin A, returning to normal after thyroid therapy. In Bright's disease, however, the level may be greatly elevated. This observation is consistent with the effects noted by Josephs,[20] who made correlative studies of the blood levels of vitamin A, carotene, cholesterol and blood fat. He concluded that there is a direct relation between vitamin A, carotene and the total lipids of the blood. Indeed, the highest carotene and vitamin A values in his series were found in conditions associated with lipemia, that is, hypothyroidism, nephrosis and xanthomatosis. His lowest values were obtained in infants with pneumonia, and in patients with cardiac decompensation or with evidence of other deficiencies. In cases of pneumonia with low values for vitamin A, low values for total lipids were also found. This was true also of the cardiac cases, but not in cases of dietary deficiencies.

Of special interest is the finding by Abels, Gorham, Pack and Rhoads[21] of low levels of plasma vitamin A in patients with cancer of the gastrointestinal tract. Their results may be related to studies of cirrhosis of the liver by Ralli, Bauman and Roberts.[22]

In summary, it may be said that with the introduction of more precise optical apparatus, such as the spectrophotometer, there is a high likelihood that relative values for vitamin A and for carotene will be available and that such values will have a very important pathognomonic significance. It will be difficult to have absolute accuracy, but this goal is not beyond expectation in the near future. Such methods bid fair to supersede the visual tests as measures of vitamin A deficiency. At the present time, however, it must be admitted that this field is just being developed by clinical investigators.

Thiamin (Vitamin B_1)

Several methods applicable on a clinical scale have been proposed for the estimation of thiamin. Notable among these are two that involve the use of micro-organisms. For example, Light, Schultz, Atkin and Cracas[23] used a fermentation test for vitamin B_1 that is applicable to many problems.[24, 25] Likewise, the growth of phycomyces has been applied by Schopfer[26] and Meiklejohn.[27] More convenient, however, are chemical procedures, notably the thiochrome assay of Jansen[28] and the test of Prebluda and McCollum.[29]

In the latter method, which has been applied extensively by Melnick and Field,[30] the urine or other material to be analyzed is first extracted with benzyl alcohol. The reaction between the vitamin and diazotized para-aminoacetophenone, described by Melnick and Field,[31] is the basis for the determination. This method is highly accurate and specific, but the technic is rather complex for ordinary clinical purposes. In general, I prefer tests based on the thiochrome conversion of Jansen, the principle of which is the oxidation of thiamin to thiochrome by an appropriate amount of ferricyanide in strongly alkaline solution. Jansen has shown that a quantitative, although not complete, conversion into thiochrome occurs under appropriate conditions. Thiochrome has the property of fluorescing as an intense blue color in ultraviolet light. The intensity of the fluorescence depends on the amount of thiochrome present. This may be measured either with a photoelectric cell or by direct visual comparison with a series of standard tubes.

The technic of this reaction has recently been surveyed by Egaña and Meiklejohn,[32] who point out that a preliminary extraction with isobutyl alcohol removes many interfering substances. The technic is complicated somewhat by the fact that certain interfering substances in pathologic urine hinder the recovery of the thiamin as thiochrome and so tend to exaggerate a paucity of the vitamin in urine from patients exhibiting profound disturbance of metabolism. Nevertheless, this method is now properly adapted for clinical observation. For a normal subject placed on a low thiamin diet, Egaña and Meiklejohn have found that in the course of a fortnight the twenty-four-hour excretion of the vitamin decreases from over 100 microgm. daily to less than 10. At this point, the urine is obviously pathologic. It may contain albumin, casts or blood, and certain chemical substances probably related to porphyrins or to indoxyl.

In my laboratory a twenty-four-hour urinary excretion of less than 70 microgm. of thiamin, as determined by the thiochrome method,[32] is considered prima-facie evidence of undoubted deficiency. Possibly this arbitrary value should be higher for men.

It is impossible to discuss the physiology of thiamin metabolism in this article, but a few illustrative results may be cited to indicate how the method may be applied clinically. Westenbrink

and Goudsmit[33] found that the urinary excretion of the vitamin depended on the amount injected. On a deficient diet, the urinary excretion decreased to a low level within three days. Likewise, Jowett[34] studied fractional urinary excretion following the administration of a known amount of vitamin. In normal subjects, the excretion for twenty-four hours varied from 80 to 300 microgm., and the great majority of cases showed over 100 microgm. for twenty-four hours' urine. When 3 to 5 mg. of pure thiamin was administered by mouth, the urine increased in concentration within the first hour after the administration, reached a peak between the second and fourth hours, and approached the normal level in about five hours. When larger doses were given, the increased excretion might extend into the second day. Furthermore, the percentage excreted depended on the size of individual doses rather than on the total dose given a day. It is interesting that intramuscular injections gave a maximal excretion during the first hour, and thereafter an excretion corresponding to that following oral administration. Curiously enough, these parenteral test doses disclosed no difference between normal and thiamin-deficient subjects, and the parenteral method was therefore considered to be of little value in differentiating normal persons from those suffering from lack of the vitamin. Pregnancy decreased the excretion of the vitamin, even in the absence of demonstrable clinical vitamin deficiency.

Obviously, the activity of the gastrointestinal tract modifies these responses considerably. Thus, Ritsert[35, 36] found a high fecal excretion amounting to 100 to 400 microgm. of thiamin in twenty-four hours in normal men. Indeed, after a single 10-mg. dose of thiamin, only about 5 per cent was found in the urine, whereas over 20 per cent was found in the feces. Obviously, much thiamin was not absorbed. Other factors no doubt enter into the picture. For example, Melnick, Field and Robinson[37] have found that vitamin B_1 is unstable in alkali and that, at the alkalinity of the small intestine, thiamin is slowly destroyed. In patients with ulcerative colitis and diarrhea, absorption is also poor.

The oral thiamin-tolerance test has been made use of by several investigators. Among these, Borson,[38] Melnick, Field and Robinson,[37] Westenbrink and Goudsmit[33] and Jowett[34] have reported interesting results. If gastrointestinal disease can be excluded, it is assumed that the recovery in the urine represents a measure of the degree of unsaturation of the patient's tissues. Accordingly, the percentage excreted is inversely proportional to the size of the dose given by mouth. The extent of the deficiency may be estimated in two ways: either by determination of the number of daily doses required for the excretion to rise to normal, or by observation of the amount failing to be excreted after a single large dose. In this way, Westenbrink and Goudsmit found that the urine normally contains over 100 microgm. a day. When 3 to 5 mg. of thiamin is given, — preferably with a morning meal, — urinary excretion is increased in one hour, reaches a peak at about three hours, and returns to normal at five hours. Occasionally, doses as large as 100 mg. are given to patients, but probably over 90 per cent of such a large dose fails to be absorbed or is destroyed in the intestine.

By these methods, definite deficiency may be detected in many chronic diseases, including thyrotoxicosis, multiple sclerosis, neuritides of various types, central-nervous-system syphilis and certain neurasthenias. Ulcerative colitis likewise tends to show a low excretion. In normal pregnancy, the urinary excretion tends to fall, even in the absence of disease or true deficiency. Furthermore, in this laboratory, Dr. R. C. Roskelley[39] has found that a considerable percentage of cancer patients show thiamin deficiency even though they may present a clinical appearance of fair nutrition.

An approximate conception of this difference between the composite thiamin-tolerance curves of 14 noncancerous and 10 cancerous patients may be formulated by plotting against the time in hours (abscissa) the rate of urinary thiamin excretion in micrograms per hour (ordinate). The following abscissas should be plotted for time (hours): 0, 2, 3, 4, 5, 6, 8 and 24. The corresponding ordinates for noncancerous persons are 4, 72, 226 (peak), 95, 88, 53, 16 and 10. The corresponding ordinates for cancerous patients are 7, 26, 46 (peak), 32, 27, 24, 14 and 9. When these two composite curves are plotted, the striking difference in their respective heights will be apparent at once. It should be noted that these curves were obtained by the feeding of 5 mg. of thiamin with a meal, usually breakfast.

Of course, many cancerous patients encountered in a general clinic suffer from thiamin deficiency per se, as evidenced by a preliminary thiamin excretion of less than 70 microgm. per twenty-four hours. Obviously, such patients show a low tolerance curve. The data summarized in the preceding paragraph, however, were derived from patients whose preliminary thiamin excretion was in all cases greater than 70 microgm. per twenty-four hours; therefore, the flat curve for cancerous persons is especially interesting and merits careful investigation of the mechanism involved.

Similarly, O'Shea-Elsom and Machella,[40] in a study of vitamin retention in patients with hepatic cirrhosis, found some diminution in the excretion

of extra thiamin. The cause of this, however, they attributed to faulty absorption.

Blood Thiamin

It is interesting that under normal conditions very little pure thiamin is found in the blood, in either the cells or the plasma. Indeed, the plasma seems devoid, or nearly so, of any thiamin derivative. The red cells, however, contain definite amounts of the enzyme cocarboxylase, which was first identified chemically as thiamin-pyrophosphate by Lohmann and Schuster.[41] Even after the administration of thiamin chloride by vein, in the course of ten minutes to an hour, the material disappears from the plasma. This is true because much of the vitamin escapes into the urine, and also because it is converted in large measure into cocarboxylase. Simultaneously, there is a rise in the cocarboxylase content of the red cells. Methods are available for estimating this cocarboxylase concentration,[42] but as yet they have not been applied extensively to clinical patients.

In a procedure recently developed by Egaña,[43] the blood diphosphothiamin and the thiamin itself are determined after separate conversion into thiochrome. In normal persons, Egaña finds that the diphosphothiamin level in whole blood is 7.0 to 8.5 microgm. per 100 cc. He finds no coenzyme in the plasma. The free thiamin reaches a concentration of 3.5 to 4.2 microgm. per 100 cc. of whole blood, and is present in both cells and plasma.*

Riboflavin (Vitamin B_2)

Riboflavin possesses several characteristic properties that are useful in its estimation. For example, Kuhn, György and Wagner-Jauregg[44] demonstrated that pure riboflavin gives off a yellow-green fluorescence on activation by light of certain wave lengths. This property has been used extensively in the estimation of the vitamin. It is also possible, as shown by Koschara,[45] to measure the vitamin concentration by the direct measurement of its color or light absorption. This method, however, has found less favor than the fluorescent one, in which the final concentration of the vitamin is determined either by comparison with a direct series of standards under monochromatic ultraviolet light or, more effectively, by the use of a fluorophotometer. Because riboflavin is sensitive to light, it is essential that examination of the vitamin be carried out under controlled illumination. Various procedures have been used in the preparation of the final filtrate for the determination. Indeed, the vitamin has been measured by its color, by the use of a step-photometer, by its fluorescence in aqueous solutions, by the color of its derivative, lumiflavin, dissolved in chloroform, and by the polarograph method. Most of these involve preliminary extraction of the vitamin. Najjar[46] has described one of the more useful of these procedures. He adds pyridine to the urine or other aqueous medium under investigation, and then separates the pyridine by salting out with anhydrous sodium sulfate. The separating pyridine contains practically all the riboflavin. Ultimately, the vitamin is extracted into butyl alcohol and measured in a fluorophotometer illuminated by a mercury-vapor bulb.

Likewise, Hodson and Norris[47] extracted the riboflavin in 0.25 normal sulfuric acid, and subsequently subjected the solution to treatment with sodium hyposulfite and stannous chloride at pH 7.

After a suitable extract is made, it is usually necessary to remove the vitamin selectively by adsorption. Accordingly, Ferrebee[48] introduced two preparations of fuller's earth, known as Floradine and Supersorb, respectively. Elution from these adsorbants was accomplished with a solution of 20 per cent pyridine in 2 per cent acetic acid. Even at this stage, however, the filtrate contains pigments that interfere with optical measurements. To remove such interfering substances, the eluate may be treated with an oxidizing agent, for example, potassium permanganate or hydrogen peroxide. A convenient modification of these methods that combines the determination of riboflavin and thiamin in food products has been described by Conner and Straub.[49] The riboflavin content of the solution is determined as follows:

> After elution of the uroflavin and subsequent oxidation to decolorize the solution, the solution is made up to volume with water, and the fluorescence measured with an exciting mercury-line beam at 4358 angstroms. The fluorometric photoelectric cells should be protected by a filter, described by Conner and Straub.[49] Turbidity of the solution or a gaseous emulsion must not be present. Under these circumstances, the relation between the fluorescence and riboflavin concentration is a linear one when suitable corrections are made for optical densities.

The urines of normal subjects frequently contain more than half a microgram of flavin per cubic centimeter,[50] and under these circumstances the urine may be diluted to the point where salts and other materials present no longer affect the fluorescence, as shown by Kuhn and Moruzzi.[51] After interfering substances have been oxidized according to Koschara's[45] procedure, the fluorescence may be measured at once. When the urine is more dilute in vitamin, some preliminary con-

*While this article was in press, there appeared two papers by Rhoads and his collaborators[65, 66] on the thiamin content of blood in leukemic patients. In this disturbance, the leukocytes and erythrocytes contain an abnormally high concentration of "combined thiamin." Consequently, the total thiamin content of the whole blood is approximately three times the normal. The ultimate significance of this important finding is not yet established. Certain cases of Hodgkin's disease and cancer of the gastrointestinal tract behave similarly.

centration of the uroflavin is necessary, such as that accomplished by the methods of Ferrebee[48] and of Conner and Straub,[49] already cited.

As a qualitative check for the presence of riboflavin, the uroflavin may be converted into lumiuroflavin by the action of light in cold, strongly alkaline solutions. Under these circumstances, a chloroform-soluble pigment that shows a faint green fluorescence is formed. This method is as yet in the early stages of development.

Henry, Houston and Kon[52] have compared the biologic method of assay of riboflavin with the fluorometric assay and have found good agreement in various milk products. So far as other methods of assay are concerned Arnold, Lipsius and Greene[53] have tested the microbiologic procedure of Snell and Strong,[54] which is based on the influence of this substance on the growth of *Lactobacillus casei*. This method is tolerably specific and much quicker than the rat-assay method, and can be carried out with very small amounts of material. The twenty-four-hour excretion of uroflavin in normal subjects varies from 700 to 1700 microgm. In general, as shown by Emmerie,[55] urinary excretion tends to follow the riboflavin content of the diet.

Physiologic Role of Riboflavin

It is known that riboflavin when phosphorylated, that is, when combined with phosphate, is utilized as the prosthetic group for several tissue-enzyme systems that are important in biologic oxidation. Some of these are described by Karrer et al.[56] Well-known metabolites, such as lactic acid, the *d*-amino-acids and glucose, depend in part on this combined vitamin for their utilization in bodily economy. For these reasons, human illness can result from lack of the vitamin. As yet, however, no extensive study has been made of its clinical applications. Sebrell[57] calls attention to the prevalence of vitamin B_2 deficiency associated with other deficiencies, notably that of nicotinic acid. In these conditions, the relief of such lesions as the vascularization of the cornea and the healing of fissures of the mouth — the so-called "perlèche" — often depend on the supply of vitamin B_2. These lesions are not relieved by either thiamin or nicotinic acid. At the moment, however, no clear-cut clinical pathologic entity unaccompanied by manifestations of other vitamin deficiency is generally recognized as specifically requiring riboflavin for therapy without other vitamins. In the mixed vitamin deficiencies, fortunately, diets that contain thiamin or nicotinic acid usually supply adequate riboflavin.

Nevertheless, there are available certain interesting observations in man that will serve as a background for future clinical studies. For example, after the oral administration of some 200 mg. of riboflavin, Klein and Kohn[58] recovered about 25 per cent from the urine as riboflavin. At the same time, the dinucleotide concentration in the erythrocytes was approximately 30 microgm. per 100 cc. However, the actual concentration of the flavin-adenine dinucleotide in urine and saliva after such a large injection of riboflavin was less than 1 microgm. per 100 cc. Obviously, the dosage given in this case must be considered unusually high, because Cowgill[59] has estimated the daily requirement of riboflavin at from 1 to 2 mg. a day for an adult. Stiebling and Phipard[60] have confirmed this value.

Blood versus Urinary Riboflavin

Axelrod, Spies and Elvehjem[61] have found that in normal subjects blood riboflavin values range between 35 and 45 microgm. per 100 cc. Surprisingly enough, approximately the same blood values were found in a group of patients with riboflavin deficiency. Apparently, the determination of the riboflavin concentration in blood or muscle is of little significance in evaluating riboflavin deficiency in man. Accordingly, it is preferable to use urinary excretion. Thus, Strong, Feeney, Moore and Parsons[62] found that the daily urinary excretion of riboflavin by normal human adults was between 500 and 800 microgm. a day. When the dietary content of riboflavin was reduced to 1 or 2 mg. a day, the urinary value soon decreased to 50 to 150 microgm.

When 5 mg. daily was given supplementary to the diet, most of it was excreted promptly. However, in the presence of vitamin deficiency, no extra vitamin was excreted in response to the reinforcement of the diet, or else the response was small and delayed. Here again, one finds that the vitamin tolerance or vitamin retention, as with thiamin, is a better and more convenient index of vitamin lack than direct determinations in the blood.

Although much further clinical work needs to be done with this vitamin, it seems likely that tolerance tests for its lack are useful in obscure cases of ophthalmologic or dermatologic nature. It is also probable that such a test may be valuable in cases of vague neurologic or psychic disturbance. It remains to be seen what the status of this vitamin is in cancer. The work of Rhoads and his co-workers[63, 64] suggests that this vitamin may be implicated in cancer of the liver, if not in other malignant processes. To test this point, tolerance

tests involving riboflavin are being made in this laboratory by Dr. Roskelley. It is apparent that patients with cancer may suffer from such vitamin deficiency, but the implications of this fact are not yet clear.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 28161

PRESENTATION OF CASE

A thirty-five-year-old clerical worker was admitted to the hospital because of abdominal enlargement.

Three years before entry, the patient, who had previously been quite well, began to have vague abdominal distention and sensations of epigastric fullness after meals, relieved by soda. There were no other symptoms. After about two years, the distention and fullness became severer, and the patient began to lose appetite. He limited his diet to fruit and vegetables. Cough, productive of small amounts of mucoid sputum, next appeared. The patient consulted his physician, and was referred to a sanatorium. Physical examination at that time showed great enlargement of the spleen, the lower pole reaching to the level of the left iliac crest. A few moist rales were heard at the left apex. A large "hemangioma" involved the left hand, in the area of ulnar-nerve distribution. The blood showed a white-cell count of 4700, with 54 per cent polymorphonuclears, 39 per cent lymphocytes, 1 per cent monocytes and 5 per cent eosinophils. The red-cell count was 4,100,000, with 82 per cent hemoglobin. The icteric index was 5.0. The blood Hinton reaction was negative. The sputum was negative. A roentgenogram of the chest showed bilateral apical mottling, reaching to the second interspace on the right and to the third interspace on the left. A roentgenogram of the abdomen showed several large areas of calcification in the lower portion. A roentgenogram of the left hand showed a rounded, laminated calcified nodule in the "hemangioma." A roentgenogram of the esophagus showed no evidence of varices. Two guinea-pig inoculations of gastric washings were negative. The patient stayed in the sanatorium five months, and then left against advice, roentgenograms of the chest showing no regression of the mottling. A month later, he came to this hospital.

The past and family histories were irrelevant. There was no known exposure to tuberculosis. The patient had not been farther south than Washington, D. C.

On entry, the patient appeared well developed and nourished. The chest was flat, with somewhat limited expansion. Krönig's isthmus was narrowed to percussion on both sides, more on the left than on the right. No rales were heard. There was an area of increased breath sounds about 2 cm. in diameter in the fourth left interspace, posteriorly. The lungs were otherwise normal. The heart was normal. The abdomen was soft, and the liver was not palpable. A large, firm, smooth mass lay in the left upper quadrant, extending halfway toward the midline and moving slightly on inspiration. There were no signs of free fluid. A soft swelling extended between the fourth and fifth fingers of the left hand, from palm to dorsum. A small, rounded, hard mass was palpable within this swelling.

The temperature, pulse and respirations were normal. The blood pressure was 100 systolic, 70 diastolic.

Examination of the blood showed a red-cell count of 4,200,000 with 83 per cent hemoglobin, and a white-cell count of 8000 with 79 per cent polymorphonuclears, 6 per cent lymphocytes, 14 per cent monocytes and 2 per cent basophils. No parasites were seen on smear. The red cells showed slight variation in shape. The serum protein was 9.4 gm. per 100 cc., with an albumin-globulin ratio of 1.09. The nonprotein nitrogen was 20 mg. per 100 cc. The van den Bergh reaction was biphasic and slightly elevated. The urine was normal. A Congo-red test showed 77 per cent retention. The tuberculin test was negative in a 1:10,000 dilution. The Frei test was negative. Gastric analysis showed 30 units of free acid half an hour after histamine.

A roentgenogram of the chest showed mottled increased density in both upper lung fields, with fine mottling in the left lower lung field. An apparent cavity was seen by fluoroscope in the right infraclavicular area. The heart was normal. The left diaphragm was slightly elevated and showed impaired motion. Roentgenograms of the upper gastrointestinal tract showed slight questionable dilatation of the folds of the lower esophagus. The otherwise normal stomach was displaced to the right by the greatly enlarged spleen. Multiple calcified mesenteric nodes were visible. Subsequent roentgenograms showed no evidence of a pulmonary cavity, and no evidence of esophageal varices.

On the seventh hospital day, peritoneoscopy was performed.

DIFFERENTIAL DIAGNOSIS

DR. JACOB LERMAN: May we see the x-ray films?

DR. AUBREY O. HAMPTON: There are only one or two films of the esophagus that show the slightest suggestion of varices; all the rest are normal. I do not believe that the patient had any varices.

What appears to be the spleen comes to the crest of the ilium and displaces the stomach medially. The liver is 4 cm. above the right iliac crest, but the diaphragm is low on both sides, so that it is not a huge liver. Examination of the chest shows what appears to be tuberculosis in both upper lobes. There is mottled density on both sides and old pleurisy at the left base quite characteristic of tuberculosis. The questionable cavity disappeared in further examinations. The lower lobes are normal. The pathologic lesions are all in the upper lobes. Then we have a film of the hands; there is no pulmonary osteoarthropathy. The areas of calcification in the abdomen, these large round masses varying from 1 to 3 cm., have the appearance of tuberculous lymph nodes.

DR. LERMAN: The differential diagnosis centers about three important findings: splenomegaly, pulmonary disease, as indicated by the x-ray film, and "hemangioma" of the left hand, which was probably incidental. I shall consider the causes of enlargement of the spleen under three main headings: infections, tumors and miscellaneous factors.

Under the heading of infection, one must consider tuberculosis (tuberculoma) of the spleen as most likely in this case. This would explain the pulmonary picture and the calcified nodules in the abdomen referred to by Dr. Hampton. However, the absence of wasting, fever and other systemic symptoms is against this diagnosis. The failure to detect acid-fast organisms and the negative tuberculin reaction in a dilution of 1:10,000 argue strongly against tuberculosis but do not rule it out. I do not favor this diagnosis. Syphilitic gumma of the spleen must next be considered. The irrelevant history, absence of syphilitic disease elsewhere and negative blood Hinton reaction rule it out. Chronic malaria may give such a large spleen, but there was no history of malaria, and the blood smear was negative for malarial organisms. Finally, one should mention kala-azar as the cause of a large spleen. It need not be considered in this case because the patient had never been outside this country and the blood smears were negative for leishmania organisms. Of the diagnoses so far mentioned, only kala-azar would explain the high serum protein. This last finding also raises the possibility of lymphogranuloma inguinale, in which an elevated serum protein is common. The negative Frei test practically excludes this diagnosis.

So far as the possibility of tumor is concerned, hemangioma suggests itself as the most likely benign tumor because of the presence of hemangioma elsewhere. There is nothing to corroborate this diagnosis, which does not explain the pulmonary findings. Malignant tumors such as reticulum-cell sarcoma, lymphosarcoma, lymphoma and endothelioma are unlikely because of the absence of systemic symptoms and of involvement elsewhere, considering the duration of the disease. A biopsy would be necessary for an absolute diagnosis. Chronic myelogenous leukemia is a frequent cause for such a large spleen. However, the absence of systemic symptoms, of severe anemia and of abnormal cells in the blood, as well as the high serum protein, excludes this disease. A cyst of the spleen is a possibility, but the description of the character of the spleen does not fit that of a cyst.

I must consider, in passing, the possibility of multiple myeloma, which is suggested by the high serum protein. There is nothing else in the description of the case that fits this diagnosis. Also worth mentioning are Gaucher's disease, hemolytic jaundice and thrombocytopenic purpura as causes of splenomegaly. There are no findings in this case to support any of these diagnoses.

There remain three diagnoses that fit this case best: amyloid disease, Banti's syndrome and sarcoid. The first two require an additional diagnosis to explain the pulmonary findings, whereas sarcoid accounts for both the splenomegaly and the pulmonary lesions.

Amyloid disease associated with pulmonary tuberculosis or nontuberculous pulmonary infection is a strong possibility. The absence of albuminuria, the high serum protein and the normal Congo-red test fail to corroborate it but do not rule it out. The enlargement of the liver mentioned by Dr. Hampton and the elevated van den Bergh reaction suggest liver involvement consistent with amyloid disease. In the early stages of this disease, there may be a high serum protein, with increased amounts of globulin.

Under Banti's disease, or splenic-vein hypertension, I am including such conditions as portal cirrhosis with splenomegaly or splenomegaly ending in portal cirrhosis, splenic-vein thrombosis and any other type of splenic-vein obstruction. The age, duration of symptoms, relative good health of the patient, slight normochromic anemia and slight leukopenia are consistent with the diagnosis. The evidence of slight liver involvement is also in favor. At times, a high serum protein with hyperglobulinemia may occur in the early stages of cirrhosis. The absence of gastric bleeding is strongly against Banti's disease. Esophageal varices have played hide-and-seek with us. The failure to find them also argues against this diagnosis. Furthermore, the presence of an associated pulmonary infection, tuberculous or nontuberculous, must be assumed, to explain the findings in the lungs.

Sarcoid would explain the large spleen, together with the signs in the lungs, although the signs are not typical. The cases that I have seen have

shown involvement around the hilar regions, with areas of increased density radiating to the lower lung fields. Moreover, the spleen is unusually large for sarcoid, which may, however, be of this size. The elevated serum protein and the hyperglobulinemia are characteristic of sarcoid. The absence of skin, lymph-node and bone involvement argues against sarcoid but does not rule it out.

Of these diagnoses, I believe sarcoid is the most likely. The other possibilities are amyloid disease and Banti's disease, associated with pulmonary tuberculosis or nontuberculous pulmonary infection.

DR. HAMPTON: I think that would be a very unusual picture for sarcoid in the chest. I do not believe that we have seen localization of the pulmonary lesion to that extent in sarcoid.

DR. LERMAN: I agree; I mentioned the fact that it is unusual for sarcoid. The lesions are usually lower and around the hilum.

DR. DONALD S. KING: Or diffuse through both lungs. We advised peritoneoscopy on this patient because he was much like the one of Dr. Robert S. Palmer's patients who was operated on for a large spleen and who had an x-ray film a good deal like this. But this lung does have lesions down toward the base.

DR. HAMPTON: A spleen as large as that in sarcoid must be rare.

DR. TRACY B. MALLORY: We have had two sarcoid spleens weighing approximately 1000 gm.

DR. LERMAN: There are cases in the literature in which splenectomy was done.

DR. KING: Dr. Palmer's case looked like miliary tuberculosis. They took the spleen out at operation, thinking that it was miliary tuberculosis.

DR. MALLORY: Dr. Benedict, do you want to tell about the peritoneoscopy?

DR. EDWARD B. BENEDICT: The liver showed multiple fine, gray, linear markings, and the spleen showed pin-point gray markings on the surface, high above the splenic notch. The spleen was enlarged to the umbilicus. The liver did not appear very large. This slide shows the appearance of the liver.

DR. MALLORY: I am quite sure if I saw the surface of the liver looking like that I should have no idea what it was.

DR. BENEDICT: This is the artist's interpretation, and I think it is accurate. I called Dr. Castleman to look at it, and as a matter of fact he said it was consistent with what the diagnosis was.

DR. MALLORY: That was a good guess.

CLINICAL DIAGNOSES

Splenomegaly and pulmonary pathology.
Sarcoid?

DR. LERMAN'S DIAGNOSIS

Sarcoid.

ANATOMICAL DIAGNOSIS

Sarcoid.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Dr. Benedict removed a small piece of the liver, sections of which showed considerable fibrosis, but no signs of caseation; it seemed to us typical of sarcoid. We have a little further confirmatory evidence. This patient was kept on the wards some weeks without much change, allowed to go home, told to rest as much as possible and to keep on a high-vitamin diet and so forth. Shortly after his return home, he developed some peculiar gastric symptoms, with almost constant nausea, and came back to the hospital again. Studies were made that offered no explanation for the symptoms. Both x-ray examination and gastroscopy were essentially negative, although I think that Dr. Benedict reported a little superficial gastritis. After a few weeks, this quieted down; the patient was again discharged and has been seen at monthly intervals up to last September. During this last period he has grown progressively better and, when last seen, expected to go back to work in a couple of days. On one entry, it was noted that he had a rather granular conjunctivitis, and a biopsy likewise showed typical sarcoid. So that we have two biopsies showing the same thing.

DR. ALFRED KRANES: Did the enlarged spleen disappear?

DR. MALLORY: There was no note on the last occasion about the spleen. It stayed large for a long time, I am sure.

DR. HAMPTON: I think that this film was taken a month later. The chest appears normal, or practically normal. It has cleared up somewhat.

DR. ALLAN M. BUTLER: Is there any comment regarding therapy for this case?

DR. KING: Symptomatic treatment is all that one can do. The disease will clear up almost always without any therapy.

CASE 28162

PRESENTATION OF CASE

A sixty-year-old Swedish watchmaker was admitted to the hospital because of diarrhea.

The patient was quite well until about two years before entry, when he began to have bouts of diarrhea. Each episode lasted three or four days, during which from five to seven urgent watery movements occurred daily. The diarrhea alternated with periods of three to five days of normal bowel movements. The patient was never constipated. On occasion, the stools were foul smelling and included mucus, but no blood was

ever noted. In the first year of the illness, the patient consulted two physicians, and was given various pills and medicines. A year before entry, following an upper respiratory infection, he began to cough up small amounts of thick sputum. He had no chest pain, and the sputum contained no blood. The cough abated appreciably after several days of bed rest, but never went away entirely. At about this time, the patient became aware of a small left inguinal hernia, which persisted. In the year before entry, the diarrhea became more frequent and severer. Occasionally, movements occurred at night. In this last year, a gnawing epigastric pain also appeared, gradually becoming worse. This pain was sometimes accompanied by cramping pain in the lower abdomen, followed by an episode of diarrhea. Occasionally, food relieved the epigastric pain, but otherwise there was no relation between the pain and meals. At times, the pain came on at night, when it radiated to the lumbar region. Throughout the illness, there was insidious progression of weakness and fatigability, and a loss of 36 pounds in weight.

On admission, the patient appeared large, powerfully built, fairly well nourished and in no acute distress. The skin was pale. The axillary and inguinal lymph nodes were shotty. The lungs were clear. The heart was not remarkable. The abdomen showed diastasis of the rectus muscles in the epigastric region. An indefinite, firm, tennis-ball-sized mass was palpable in the right upper quadrant, moving on respiration. A small, reducible indirect hernia was present in the left inguinal region. A firm, moderately hypertrophied prostate was palpable by rectum.

The blood pressure, pulse, temperature and respirations were normal.

Examination of the blood showed a red-cell count of 3,800,000 with 8.5 gm. hemoglobin, and a white-cell count of 18,300 with 66 per cent polymorphonuclears. The urine showed a trace of sugar. The stools were liquid brown and guaiac negative. Stool culture was negative for pathogens. The serum protein was 4.9 gm. per 100 cc.

Roentgenograms of the large bowel showed a ready flow of barium through the rectum and sigmoid to a point in the midtransverse colon beyond which the barium would not pass. At this level, there was a constant filling defect, with a scalloped, irregular polypoid margin. The folds of the mucosa appeared markedly thickened for a distance of 5 cm. beyond this place. In another examination, barium flowed readily through the sigmoid and transverse colon to outline a cone-shaped narrowing in the region of the hepatic flexure. There were two nodular filling defects at the proximal end of the area of obstruction. Apparent mucosal markings remained in the area of narrowing, arranged in concentric rings at the distal widest point. A roentgenogram of the chest showed no evidence of disease.

On the tenth hospital day, an operation was performed.

Differential Diagnosis

Dr. Allen G. Brailey: This history presents a classic example of slowly developing obstruction of the large bowel. The exact mechanism of such recurrent bouts of diarrhea is not known, but it is likely that the irritation of the obstructing lesion, in addition to the irritation of fecal material behind the obstruction, produces an increase of tonus of the muscular wall and more and more vigorous peristalsis, until finally the obstruction is overcome. The abnormally vigorous peristalsis then results in diarrhea, just as it does when produced by any other cause. After the bowel is emptied, a period of rest ensues until the accumulated bowel contents start the cycle over again. The bouts of diarrhea occurred at evershortening intervals, and the muscular activity of the bowel proximal to the obstruction became more and more vigorous until actual colicky pain appeared. Nothing is said about loss of appetite, but we know that such an interference with normal intestinal motility invariably results in anorexia, and this is borne out by the fact that the patient was reported to have lost 36 pounds in weight. The malnutrition that resulted from the anorexia probably accounted for his weakness and fatigability, his anemia and his lowered serum protein, although there may have been other causes for these impairments of health.

This train of events was set off by an obstructive lesion of the midtransverse colon whose x-ray description is somewhat unusual. Have you anything further to say about that, Dr. Hampton?

Dr. Aubrey O. Hampton: I remember the films very well, and I know the answer. The conical defect with multiple small, round, filling defects in the transverse colon was definitely unusual. We did not demonstrate the whole lesion, because we could not get barium beyond the point of obstruction, but the distal margin did not show the usual picture of carcinoma. It had too many fine, irregular projections from it.

Dr. Brailey: Was there evidence of polyps anywhere else?

Dr. Hampton: There were no other polyps. These polyp-appearing things were all grouped together in one spot, but we could not tell whether they were continuous or not.

Dr. Brailey: Do you think that the mucosa was normal? It was not destroyed?

Dr. Hampton: In the area near the polypoid

defects, it was normal, but toward the obstruction it was lost in a mass of polypoid defects.

DR. BRAILEY: Our first problem is to decide whether this was a lesion that began in the mucosa or whether it was intramural in origin. The statement is made that "the stools were liquid brown and guaiac negative." If the stools were persistently guaiac negative, they provide evidence of great importance in deciding the nature of this lesion. How many stools were examined?

DR. TRACY B. MALLORY: One stool was examined. The other stool was cultured but not tested for guaiac.

DR. BRAILEY: That is too bad. I presume one might have an occasional stool with a negative guaiac reaction, but certainly it is very rare in carcinoma that has developed to the point of obstruction. The mucosa is destroyed, and oozing must occur.

I assume that this observation can be trusted, and we can therefore exclude practically any lesion, such as carcinoma, that arose in the mucosa or destroyed the mucosa, for all such lesions ooze blood and most if not all the stools would show the presence of occult blood. If I do not lose my courage and am consistent with this line of reasoning, the lesion developed within the wall of the bowel. It might have been tuberculosis. Although the x-ray appearance was not very suggestive of tuberculosis, I do not believe that this rules it out. On the other hand, tuberculosis almost invariably involves the mucosa with ulceration at an early stage; it very rarely develops in a man of this age who has no evidence of tuberculosis in the chest, and I therefore discard tuberculosis as a likely possibility. I believe that it is much more probable that this man had a new growth as the cause of his obstruction. If we must exclude primary carcinoma for lack of bleeding, we are left with metastatic tumor, which is too unlikely to be considered further, and with the various sarcomas that may develop from bowel-wall structures. These include leiomyosarcoma, angiosarcoma, sarcomas arising from nerve tissue and various types of lymphoblastoma. It is obvious that this man required an operation. It is also clear that a final diagnosis could not be made without pathological study. However, I think that lymphosarcoma is the best bet.

DR. CHESTER M. JONES: I should like to disagree with Dr. Brailey. We have been surprised at the number of patients with carcinoma of the stomach and bowel who for days on end have had guaiac-negative stools. No diagnostic inference can be placed on that, even if it were correct. Dr. Hampton points out that the relatively low red-cell count suggests that the stool report was not correct. Even if the anemia were based on malnutrition, it does not to my mind rule out cancer in any way.

It is a bit interesting to know the cause of the epigastric pain. The patient had two sets of symptoms. One set appeared quite late, and one had persisted for two years.

DR. WYMAN RICHARDSON: May I add to that statement the fact that the patient had not only a red-cell count of 3,800,000 but a hemoglobin of 8.5 gm. This means that he had a very severe hypochromic anemia, which further means he had lost blood from his bowel no matter whether the stools were guaiac negative or not. There is no question that this lesion had been bleeding — if these figures are correct, I hasten to add.

DR. BRAILEY: I started out with the assumption that there was no bleeding, but certainly with only one stool recorded I cannot maintain that argument. If we concede the bleeding, I should put my money on carcinoma rather than anything else.

DR. HAMPTON: We presented the case in our conference; I have forgotten the whole discussion, but I do not remember seeing a carcinoma with obstruction of this appearance, with these multiple, small, rounded defects as though there were many polyps in one place in the bowel — a picture of local polyposis, which I have never heard of, and at the same time a conical obstruction instead of a transverse, circular one. I do not know what our conclusions were, but I am interested in knowing what the histology is going to be.

DR. MALLORY: On the x-ray report, it was stated, "Probably carcinoma, but might well be lymphoma."

DR. HAMPTON: I think we hedged quite a bit; I should do so.

DR. JACOB LERMAN: Was there no comment about the mass that moved on respiration? If it was in the colon, it certainly would not move on respiration.

DR. HAMPTON: I disagree — the colon does move with respiration.

DR. BRAILEY: I am interested in Dr. Jones's comment that in frankly ulcerative carcinoma one can have repeated stools without blood in them.

DR. JONES: I did not say exactly that. I said that patients with cancer of the stomach or intestine — not, frankly ulcerative cancer — may go from days to weeks with no blood in the stools.

DR. BRAILEY: When the lesion is large enough to obstruct the bowel?

DR. JONES: I should not hedge on it a bit.

DR. CLAUDE E. WELCH: The Medical Department told us that this man had cancer of the colon. We did not see any reason to doubt the diagnosis and operated, with a two-stage resection. At the time of the ileocolostomy, a huge mass was located directly over the duodenum. The patient survived the first stage, and about two weeks later a resection was done. At the time, we observed considerable fixation of the mass posteriorly. It was hoped that this might turn out to be inflammatory. By the end of the resection, however, it was evident that there was considerable extension of the disease into the pancreas and that the wall of the duodenum was involved; a few nodules were found on the stomach. The main mass was taken out, but we knew we had left tumor behind.

CLINICAL DIAGNOSIS

Carcinoma of colon.

DR. BRAILEY'S DIAGNOSIS

Lymphosarcoma of colon.

ANATOMICAL DIAGNOSIS

Carcinoma of colon.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The specimen showed a very extensive carcinoma of quite low-grade malignancy. It involved 12 cm. of the bowel. Above the mass, the mucosa was very markedly edematous, — in fact, in some places more than 1.5 cm. in thickness, — but that could not explain the x-ray findings because the radiologists never saw the proximal side of the lesion. There were numerous polypoid tumor excrescences along the distal margin of the tumor, which I suppose they saw.

DR. HAMPTON: I saw the specimen, and I thought there were some fairly long mosslike strands of carcinoma protruding from the margins that probably floated in the barium.

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SELECTEES AND THEIR PHYSICAL FITNESS

The successful waging of any war depends on many factors. One of the more important is the physical fitness of the combat personnel. Much has been said concerning the health of the young men of this country, and there seems to be a rather general belief that they are strong and healthy. It has been claimed that the United States is a nation of athletes. But to be athletic does not necessarily imply that one can come up to the physical standards of the Army of the United States or the United States Navy. One well-known professional football player was recently rejected by the Army for malignant hypertension. Furthermore, two decades ago, a noted collegiate football player successfully represented one of the large universities for four years, even though he was known to have a high-grade mitral stenosis, which was proved at autopsy a few years later. In the same era, one of the country's most renowned fencers had had infantile paralysis in early childhood.

Adequate and authoritative figures concerning the health of the Nation so far as the armed forces are concerned have heretofore been difficult to obtain, and it should be remembered that a really true picture can be had only from the collective data obtained from the selective-service boards, the Army induction centers and the certificates of disability discharge after induction, with the exception, of course, of those discharges due to injuries in line of duty.

A preliminary survey[1] covering the first two types of examination is now at hand. It is illuminating but not encouraging. Fifty per cent of the approximately 2,000,000 registrants who were examined prior to May 31, 1941, were found unqualified for general military service by selective-service boards and Army induction centers because of physical, mental or educational defects or a combination of these. Twenty-five per cent were considered unsuitable for any type of military service. The requirements for the Army and Navy are rigid, but certainly not unduly so. That roughly half our young men should be unsuited for military service does not reflect too well on the state of health of the Nation, and it should be remembered that this survey took no account of the hundreds of discharges for physical or mental handicaps that were missed during the preliminary examinations and that came to light only after a few weeks or months in camp.

Nor does one gain much solace from the breakdown of the figures. "Based on the major defect or principal cause of rejection, dental defects account for . . . 20.9 per cent of the 900,000 registrants not qualified for general military service. . . ." It is probable—indeed almost certain

—that nearly all such defects can be remedied or could have been prevented; furthermore, it should be noted that these official figures do not substantiate a claim made before the Massachusetts Dental Society[2] that but 2 per cent of the registrants were not accepted because of dental defects. Next in order as causes for rejection came defects of the eyes and diseases of the cardiovascular system,—13 and 10 per cent, respectively,—and it is not likely that many of these disorders are remediable or were preventable. Then follow musculoskeletal defects, venereal diseases, mental or nervous disorders, hernias and defects of the ears and feet, each roughly 5 per cent. Diseases of the lungs, including tuberculosis, were a cause for rejection in but 2.9 per cent—a creditable figure, although it should be remembered that registrants of some states had no x-ray films taken prior to induction.

Exactly how many of these rejected men can be rehabilitated is impossible to say. The survey states, "Of the 900,000 who have been classed as available for limited military service or disqualified for military service, an estimated 200,000 can be completely physically rehabilitated for the performance of general military service." The President has charged the Selective Service System with such a rehabilitation program. It should be noted, however, that no provision has yet been made whereby the man enlisting can have remediable defects corrected if he voluntarily does not have the money to do so himself.

Three things seem clear: an appallingly large number of young men are unfit for military service; many of the nonremediable disqualifying defects could have been prevented; and rehabilitation should benefit not only the armed forces but the Nation as a whole—whether at peace or at war. It is to be hoped that the physicians, dentists and hospitals of this country will aid in the correction of these defects.

References

1. Analysis of reports of physical examination: summary of data from 19,923 reports of physical examination. Medical Statistics Bulletin No. 1. National Headquarters, Selective Service System. Washington, D. C. November 10, 1941.
2. *Boston Herald* (February 4, 1942: page 17).

AMERICAN INSTITUTE FOR PSYCHOANALYSIS

Orthodoxy and the scientific attitude can scarcely be considered compatible. Earnestness in the desire to seek the truth and willingness to discard supposed facts when they cannot be substantiated must be the foundation for honest, progressive scientific work. A justifiable criticism of some psychoanalysts of the Freudian school or of some of the psychoanalytic societies is that they insist on the orthodoxy, the incontrovertible correctness, of Freud's fundamental concepts. Their zeal in supporting their master's teachings sometimes exceeds what Freud himself probably would have thought permissible. If a theory or a hypothesis is sound, it may be examined searchingly without danger to its validity and without embarrassment to its proponents. When the advocate of any thesis reacts antagonistically to a questioning analysis of the soundness of his doctrine, it is fair to doubt his fitness for scientific investigation.

Whether for personal reasons or because of an impersonal, objective interest in liberal, scientific progress, a number of the members of the New York Psychoanalytic Society last spring severed themselves from the society and established the American Institute for Psychoanalysis. According to a statement issued by them, they could no longer put up with what they termed the "dogmatism" of certain elements within the society, and they believed that the future of psychoanalysis and psychoanalytic education would be jeopardized if directed with an ex-cathedra attitude.

In the organization of the new institute, the plan is to teach psychoanalysis as "a young science, still in an experimental stage of its development, full of uncertainties, full of problems to which anything approaching final and conclusive answers is still to be sought."

The disagreements and wrangling within a particular society may be considered inevitable and healthy for the vitality of the organization. The schism here referred to may be of no general importance. Since it is well known, however, that there is a tendency in some psychoanalytic circles

to defend some of Freud's hypotheses with a bias of almost religious faith, it is well for the future of psychoanalysis if some of Freud's followers have inquiring minds. No really great teacher in medicine ever wanted investigation to go forward with the provision that the soundness of his own contributions was to remain eternally indisputable.

Freud was a man, not a deity, and he allowed himself the privilege of changing his mind. A belief that his observations and conclusions were unswervingly accurate denies human fallibility. Even in the scientific world, the power and influence of personality can be tremendous. Most men admire the attributes of leadership and superior intellect, and for many physicians who cannot accept the tenets of a theological system, the human need for security is somewhat satisfied if they think that they see ultimate truth in a supposedly scientific cloak. Combine this admiration and this need with suggestibility, which is present in all of us to more or less degree, and the critical faculty is not likely to be dominant. It is good to see that dissidence, even though possibly arising from personal resentment, may begin to break the spell of Freud's personality.

MEDICAL EPONYM

Niemann-Pick Disease

"Ein unbekanntes Krankheitsbild [An Unrecognized Syndrome]" was described by Dr. Albert Niemann (1880), assistant in the Berlin pediatric clinic of Professor Czerny, in the *Jahrbuch für Kinderheilkunde* (**79:** 1–10, 1914). A portion of the translation follows:

> It is my present desire to direct the attention of my colleagues, particularly the pediatrists, to a very remarkable syndrome, which I speak of as unrecognized not only because I myself have never seen it before, but also because I have looked in vain throughout the literature for a description of it. . . .
>
> The victim of the disease was a female child, aged seventeen months . . . who had been sick from the beginning of the second month of her life and whose chief symptom, even at that time, had apparently been a tumor, presumably of the spleen. . . .
>
> We found a wretchedly nourished child, apathetic, underdeveloped, with wide-open fontanelles, unable to stand or walk. . . . The most striking finding on inspection was the tremendously enlarged abdomen (circumference, 50 cm.). This huge swelling consisted of liver and spleen. The spleen extended far below the navel, as did the liver, the lower border of which was a fingerbreadth above the right anterior superior spine. The veins of the belly were markedly dilated, there was some demonstrable free fluid in the abdomen, and there were signs of congestion elsewhere: a catarrhal condition of the lungs, edema of the feet and eyelids. . . . There was no jaundice. . . . The congestive phenomena increased, diarrhea supervened, and finally after a stay of four weeks in the clinic, exitus occurred. . . .
>
> Autopsy showed . . . a very large spleen, not excessively hard, with a rather spotted surface. Section revealed yellowish white foci, the size of a lentil, frequently confluent, between which only very narrow bands of normal splenic substance persisted, so that the cut surface looked whitish yellow when seen from a distance. . . . The liver was likewise markedly enlarged, with the color and markings of fatty degeneration such as that seen in cases of phosphorus poisoning. . . . The abdominal lymph nodes were not only moderately enlarged, but also showed a peculiar yellow fatlike color and were rather soft in consistence. . . .
>
> Microscopic examination of the spleen showed . . . almost the whole structure to be replaced by peculiar cells . . . very large, irregular in shape, irregularly distributed, sometimes crowded together, sometimes separated from each other. They contained a small, round nucleus. . . . Exactly similar cells were found in the liver . . . and . . . also in the abdominal lymph nodes. . . . I should like to propose the name *grosszellige Drüsenmetamorphose* [large-cell glandular metamorphosis] for this disease.

Ludwig Pick (1868), director of the Pathological Anatomical Department of the Municipal Hospital, Friedrichsheim, Berlin, presented a communication, "Zur pathologischen Anatomie des Morbus Gaucher [On the Pathological Anatomy of Gaucher's Disease]," before the *Berliner medizinische Gesellschaft* on October 11, 1922. His remarks and the discussion that followed appear in the *Medizinische Klinik* (**18:** 1423 and 1449, 1922). A portion of the translation follows:

> In a case of splenomegaly and hepatomegaly in a seventeen-month-old female child, described by Niemann in 1914 under the title "An Unrecognized Syndrome," the enlargement of the organs was due to an infiltration of lipoid (phosphatid)-bearing cells, as Pick was able to show on subsequent examination of Niemann's material. This case, together with similar observations reported by Siegmund and American authors (Knox, Wahl and Schmeisser) belongs in a special group of lipoid-cell splenohepatomegaly in children, in which the lipoid cells are found in a considerable number of other organs (heart, dura, kidneys and so forth).

An exhaustive critique of the subject is given by Pick under the title "Der Morbus Gaucher und die ihm ähnlichen Erkrankungen [Gaucher's Disease and Similar Maladies]" in *Ergebnisse der inneren Medizin und Kinderheilkunde* (**29:** 519–627, 1926).

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

CASE HISTORY: ACUTE INVERSION OF THE UTERUS, CAUSING HEMORRHAGE AND DEATH

A thirty-year-old multipara had had adequate prenatal care and was delivered at term of a living child. Labor, which had been induced for reasons not stated, lasted eleven hours and forty minutes. The delivery was a breech and was said to have offered no difficulty. The condition of the mother following delivery was satisfactory. The placenta was not delivered immediately, and Credé's method was resorted to, with the result that the uterus became acutely inverted. The placenta was peeled from the uterine wall. The bleeding was tremendous, and the patient's condition became grave. A tourniquet was placed about the inverted portion of the uterus, and the patient was given 750 cc. of whole blood. In spite of this, she died before the uterus had been replaced.

Comment. Inversion of the uterus is always a very serious complication. In this case, it was undoubtedly induced by undue attempts at Credé's method. That the placenta was still attached when the uterus became inverted is evidence that no separation had occurred before the procedure was attempted. Such attempts should never be made until there is evidence that the placenta has separated. Had this placenta been left, it is quite probable that it would have separated spontaneously and delivered itself without undue loss of blood. It is also probable that had this uterus been replaced under anesthesia as soon as it appeared at the vulva, the subsequent hemorrhage might have been averted. It is often impossible, however, to replace an inverted uterus manually. In such a case, laparotomy is indicated.

Cases of chronic inversion of the uterus are extremely rare, since most patients with uteri that become inverted and are not replaced die of hemorrhage. However, chronic inversion has been known to exist for months. For example, when one patient who had had several hemorrhages after delivery was finally seen in consultation about three months after her baby was born, a diagnosis of chronic inversion was made. She was operated on, the uterus was replaced, and the patient has since had a living child.

The fatality in the case presented seems to have been avoidable.

"PROBLEMS OF TUBERCULOSIS UNDER WARTIME CONDITIONS"*

Although tuberculosis is not popularly identified as one of the four horsemen of the Apocalypse, it is unquestionably one of the major pestilences of war; there is no more sensitive barometer of national privation and suffering. In World War I, the tuberculosis mortality in all combatant countries rose within the first year and climbed steadily until after the armistice. In France, England and Germany, the rates practically doubled, and even in this country the mortality in 1918 was 50 per cent higher than that in the preceding few years. In the United States, the total deaths from tuberculosis at least equaled the losses in battle in any year of the war.

Incomplete reports from Europe show that tuberculosis had again definitely increased in 1940, and preliminary data here indicate that nearly half the states experienced a slight rise in mortality in 1941. With the prospect of a war longer, more inclusive and far more exhausting than the last, it is high time that we define the problems of tuberculosis under wartime conditions and organize all available control measures in the civilian population as well as in the armed forces.

Essentially, the problems of control are the same in war and in peace: early recognition of cases, prompt hospitalization of those needing treatment, examination of family contacts, maintenance of adequate nutrition, good housing and a reasonable sense of security. The great problem is how to attain a semblance of such conditions with restricted food supplies in a situation that calls for the expenditure of the utmost effort of which we are capable.

The first line of defense is the maintenance, at all costs, of the very effective control organization that has been built up in the last forty years. Although our sanatoriums and clinics have not been the only factors responsible for the decline of 80 per cent in the tuberculosis mortality in that period, they are the most effective weapons we possess for checking any upsurge of the insidious enemy. Prevention, far more than treatment, has been responsible for the gains that have been made, and so long as we prevent the spread of infection from open cases we shall be able to check the infiltration of our population that results in ultimate disaster.

At the beginning of the present war, the English promptly discharged to their homes a large number of patients in tuberculosis santoriums to make room for expected military casualties. When it was found that the beds were not needed, these tuberculosis cases were gradually returned to their hospitals, but the tuberculosis service was seriously disrupted and the damage that resulted from returning a large number of patients with contagious lesions to their homes and communities is hard to estimate. It is to be hoped that we profit by our neighbor's experience and retain, so far as possible, the exceptionally adequate sanatorium system we have built up.

Recruitment of physicians and nurses for military needs is bound to throw additional burdens on local boards of health, which have the primary legal responsibility for tuberculosis control. It is essential that reporting of cases be prompt and complete and where every doctor's load has been doubled he must depend more and more on the local public-health nurse for the follow-up and instruction of tuberculosis patients and their families that are so vital a part of prevention. When the patient has gone

*A "Green Lights to Health" broadcast given through Station WAAB by Dr. Alton S. Pope on Saturday, February 7, and sponsored by the Public Education Committee of the Massachusetts Medical Society and the Massachusetts Department of Public Health.

to the sanatorium, it is often the nurse's responsibility to see that the other members of the family come in for x-ray examination, and when necessary, receive adequate aid during the sickness of the wage earner.

Nutrition is perhaps the most vital factor in tuberculosis control in wartime. In the last war, the tuberculosis mortality was in general proportional to the inadequacy of the food supply, and in the neutral countries a rise became noticeable only when meat and dairy products had been depleted by combatant neighbors. Nutrition has always played an important part in the treatment of tuberculosis, and there is every reason to believe it can play an equally significant role in prevention. A striking example of the correlation between privation and tuberculosis mortality is the situation in Germany twenty years ago. Three years after the armistice, the mortality had fallen nearly to prewar levels, but in the economic collapse of 1922–1923, the food shortage became almost as acute as it had been in 1918 and the tuberculosis mortality promptly rose about 50 per cent.

During the recent depression in the United States, tuberculosis experts freely predicted a general rise in the incidence of the disease, which to date has not materialized. The most reasonable answer seems to be that in spite of the great reduction of income for most of our population, the people on relief were on the whole more adequately fed than they had been during some periods of prosperity. In other words, malnutrition to be a factor in the activation of tuberculosis must apparently reach a certain critical level, and if we can prevent its reaching that point by proper husbanding of our supplies and by judicious balancing of our diets, there is reason to hope that we can minimize one of the hazards that has seemed an inevitable part of war.

In no field of social welfare has this country been so backward as in housing, and it is doubtful whether any social factor more seriously complicates tuberculosis control under war conditions. The spread of tuberculosis depends on two things: the transmission of the causative organism, and the resistance of the human host. Obviously, the closer the contact between the open case and a susceptible host, the more rapidly will the disease spread, and no factor is more favorable to such rapid transfer than overcrowding in poorly lighted and inadequately ventilated tenements. It is, of course, too late to correct such a situation in the face of more pressing demands, but we can at least make every effort to discover active cases of tuberculosis and remove them to a safer environment.

Difficult as it is to maintain the existing facilities for the prevention and treatment of tuberculosis under wartime conditions, those very conditions open certain new avenues of attack. First among them has been the opportunity to secure preinduction x-ray examinations of practically all men entering the armed forces of the country. Because the Army Medical Corps was not prepared to undertake these examinations in Massachusetts when the Selective Service Act went into effect in the fall of 1940, the State Department of Public Health took on the task through its field clinic unit, by means of portable x-ray apparatus. Films were furnished by the Army and exposed and interpreted by the clinic staff. In the course of a year, 10,000 members of the Massachusetts National Guard and 23,000 selectees were x-rayed, and 134 cases of significant tuberculosis were found, an incidence of approximately 0.5 per cent. With the installation of its own apparatus, this work has now been taken over by the Army Medical Corps, and the preliminary screening of all recruits promises to reduce substantially the future needs for treatment and compensation of soldiers disabled by tuberculosis — an expense that has reached a cumulative total of nearly $1,000,000,000 since the last war.

Treatment for recruits found to have tuberculosis is fortunately immediately available in Massachusetts. Some, however, who are disqualified by a history of tuberculosis or inactive lesions offer a real problem in rehabilitation. The New England Rehabilitation Center at Rutland has limited facilities for the training and placement of suitable candidates, but a problem remains that is a real challenge to boards of health and especially to voluntary tuberculosis associations.

The staggering demands made on industry for munitions, equipment and supplies of every description have made employers receptive to procedures that promise to improve the health and efficiency of their workers and thereby reduce the labor turnover. In the textile, boot and shoe, and some other industries, it has been possible to make arrangements for mass x-raying of certain groups of employees for tuberculosis case finding. Consent of the workers has been obtained through their labor unions, and reports of the findings are given to the employees only. In the groups examined, the incidence of tuberculosis has not been high, — 1.5 per cent, including healed cases, — but the active cases found are at a stage favorable for treatment and a certain number of foci of infection can be removed from the factories. Even more encouraging has been the arrangement by a few firms for the preemployment x-ray examination of their own employees. It is quite possible that such control measures, which have proved their value under the pressure of wartime production, will be accepted as an essential part of our program for the elimination of tuberculosis when a return to normal living has again made that aim a rational objective.

DEATHS

DIEZ — M. Luise Diez, M.D., of Boston, died April 12. She was in her sixty-fourth year.

Dr. Diez received her degree from the Woman's Medical College of Pennsylvania in 1903. Since 1929, she was director of the Division of Child Hygiene of the Massachusetts Department of Public Health. Dr. Diez was a member of the executive committee of the Massachusetts Child Council and of the Committee on Maternal Welfare of the Massachusetts Medical Society, a fellow of the American Public Health Association and a lecturer on child hygiene at the Harvard School of Public Health. She was a member of the Massachusetts Medical Society and the American Medical Association.

GALVIN — William Galvin, M.D., of North Adams, died April 8. He was in his eighty-fourth year.

A native of Troy, New York, Dr. Galvin received his degree from the University of Vermont College of Medicine in 1892. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

He is survived by a niece.

WAR ACTIVITIES

Decontamination of Eyes after Exposure to Lewisite and Mustard Gas

Since publication of the Office of Civilian Defense handbooks, *First Aid in the Prevention and Treatment of Chemical Casualties* and *Protection Against Gas*, further

experience has shown that the 2 per cent solution of hydrogen peroxide recommended for the treatment of eyes following Lewisite or mustard-gas burns may be injurious if used undiluted. The Chemical Warfare Service now recommends a single instillation in the eyes of a 0.5 per cent solution of hydrogen peroxide as soon as possible after contamination. This solution may be prepared by diluting one part of a 2 per cent solution with three parts of water, or one part of a 3 per cent solution with five parts of water. The solution usually found in drugstores is the U.S.P. strength (2.5 to 3.5 per cent). A 0.5 per cent solution of potassium permanganate has also been found effective as an eye instillation following exposure to these gases.

In planning decontamination stations, the Medical Division, Office of Civilian Defense, recommends that provision be made near the entrance of the second or shower room for the irrigation of the eyes of contaminated persons. The schematic sketch of a decontamination station in the official publications mentioned above shows that irrigation of the eyes should be carried out in the dressing room, whereas, more properly, this should be done in the second or shower room before the bath is given. Delay until the patient reaches the dressing room may result in serious injury to the eyes.

MISCELLANY

NOTE

Harvard Medical School awards totaling $6100 were recently announced by Harvard University. Scholarships effective February, 1942, are as follows: David Williams Cheever Scholarship to Robert Paine, of Memphis, Tennessee; Charlotte Greene Scholarship to Sheridan S. Evans, of Iuka, Illinois; George Haven Scholarships to Lyndon R. Barnett, of North Stratford, New Hampshire, Albert C. Biegel, of Denver, Colorado, Edward L. Burwell, of Porterville, New York, Harvey R. Butcher, of Adrian, Missouri, John W. Harris, of Allston, Massachusetts, Felix Heimberg, of Dorchester, Massachusetts, Peter J. Koeniger, of Woodhaven, New York, Paul J. R. Schlessinger, of Pawtucket, Rhode Island, Chandler A. Stetson, Jr., of Brunswick, Maine, Arthur W. Trott, of Wollaston, Massachusetts, and Edward P. Wallace, of Newton Center, Massachusetts.

In addition, fellowships effective September 1, 1942, were awarded as follows: Jeffrey Richardson Fellowship to John E. VanderLaan, of Muskegon, Michigan; James Jackson Cabot Fellowship to Walter E. Knox, III, of McCook, Nebraska; George Cheyne Shattuck Memorial Fellowship to John M. Weller, of Ann Arbor, Michigan; Charles Eliot Ware Memorial Fellowship to Arthur C. Guyton, of Oxford, Mississippi; John Ware Memorial Fellowship to Israel H. Scheinberg, of New York City; DeLamar student research fellowships to Robert L. Berg, of Spokane, Washington, Avram S. Goldstein, of New York City, Irving M. London, of Malden, Massachusetts, and Roger W. Morrison, of Pittsburgh, Pennsylvania.

CORRESPONDENCE

SULFANILAMIDE-POWDER SPRAY

To the Editor: In a letter published in the November 14, 1940, issue of the *Journal*, one of us (N. C. S.) suggested the use of a sulfanilamide spray in the treatment of colds and sore throats. Again, in the September 11, 1941, issue, we published the results of its use for the treatment of colds among the children at the Putney School. This report covers the recent fall and winter term at the Putney School.

Up to January, 1942, we had been using a solution of sulfanilamide, dissolving either the tablets or the powder in hot water. They did not dissolve completely, and the undissolved particles continually clogged the atomizer, whose use was thus rendered difficult and unsatisfactory. Since the beginning of the year, we have been using a sulfanilamide-powder spray, blowing the powder into the nose or throat as the case might require. This has solved the difficulty and is much more efficient. Colds that used to drag on for a week or ten days and were often followed by a long period of coughing have been almost completely eliminated. There were two cases of early otitis media that progressed no farther than to a reddening of the drums. There have been no cases of swollen cervical lymph nodes; this is somewhat significant, since both otitis media and enlarged cervical nodes have been very common in this area during the winter.

Children seem to respond better and more quickly to the spray than adults do. This may be because the nasal and pharyngeal tissues are healthier and have less scar tissue.

Sulfanilamide spray probably has no effect on the virus that causes the cold, but is markedly effective against the secondary invaders. A pure virus cold, if there is such an entity, is probably of very short duration and causes only a temporary congestion.

The following is a comparison of the days lost because of colds during the two and one-third school years, when neither the liquid nor powder spray was used, with the period from January, 1941, to April, 1942, when we were using the spray:

1938–1939 (112 pupils)	
Fall term	94 days
Winter term	104 days
Spring term	19 days
1939–1940 (122 pupils)	
Fall term	180 days
Winter term	128 days
Spring term	39 days
1940–1941 (136 pupils)	
Fall term	104 days
Winter term	89 days
Spring term	13 days
1941–1942 (145 pupils)	
Fall term	56 days
Winter term	15 days

The apparent effectiveness of the sulfanilamide-powder spray, used during the recent winter term, is obvious.

At Putney School, every child is inspected every day, and the slightest sign of a cold is treated immediately with the sulfanilamide-powder spray. The treatment is continued every two or three hours for forty-eight hours, or until the cold has cleared up.

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REPORT OF MEETING

CHELSEA NAVAL HOSPITAL

At a regular monthly meeting of the Chelsea Naval Hospital on November 14, Dr. Maxwell Finland, of the Boston City Hospital, spoke on "Recent Advances in the Treatment of Pneumonia." In introduction, Dr. Finland recalled that sulfanilamide had saved certain patients who

failed to respond to specific antiserum; that sulfapyridine had a more marked effect on the pneumococcus but also resulted in more toxic reactions, which often caused earlier cessation of therapy than was considered optimal; that sodium sulfapyridine allowed parenteral administration of this drug during the critical vomiting period; that sulfathiazole caused only half as much nausea and vomiting but that larger doses were necessary on the whole to maintain similar blood levels, because of the more rapid metabolism of this drug; and that sulfadiazine results in nausea and vomiting in only 10 per cent of patients, and is generally a less toxic and more effective drug, but is still not ideal. Sulfadiazine is like sulfathiazole — and in direct contrast to sulfanilamide — in its negligible effect on erythrocytes. Agranulocytosis is not unknown in these two more recent compounds, especially after long periods of therapy, and toxic rashes also occur in 4 to 5 per cent of cases under the same circumstances.

The most serious complications are those involving the urinary tract. Fortunately, however, large amounts of fluids can be administered with sulfathiazole and sulfadiazine, without excretion of the drugs in proportional amounts — as with sulfanilamide. Also, these compounds have the advantage of being more soluble in the acetylated form. Sulfapyridine usually causes pain and hematuria as initial manifestations, and the crystals are deposited below the level of the tubules, thereby allowing early diagnosis and lavage. Sulfathiazole therapy, on the other hand, may result in anuria without any previous manifestations, because its crystals may be deposited in the tubules themselves. Sulfadiazine may also cause anuria, but only rarely if the urinary output is kept above 1500 cc. per twenty-four hours.

In a recent series at the Boston City Hospital, the gross mortality with sulfadiazine was only 10.7 per cent. For patients under fifty years of age, it was 2.9 per cent, and in the nonbacteremic cases 7.6 per cent. This contrasts with 21.6 per cent for patients over fifty years, and 24.2 per cent for those with bacteremia. Nineteen per cent of the patients had bacteremia. The mortality in the armed forces during the present war, therefore, should not exceed 2 per cent, in contrast to that of 25 per cent in World War I, it was estimated.

As a result of experiments on the relative efficacy of the four common sulfonamide compounds on the pneumococcus, hemolytic streptococcus, *Staphylococcus aureus* and the Friedländer bacillus, — as well as on their toxicities, — it was concluded that sulfadiazine is thus far the drug of choice in all pulmonary infections.

Specific antipneumococcus serum is still useful in cases in which the responsible bacterium becomes resistant to chemotherapy. The only other reason for substituting serum for drug therapy is the onset of serious toxic symptoms, although serum may be a useful adjuvant when there is a second positive blood culture or a very severe bacteremia. Second blood cultures should always be taken when the fever lasts more than twenty-four to thirty-six hours on chemotherapy. Chemotherapy with the sulfonamides may be started with a low leukocyte count, so long as it is not due to previous administration of the drug and there are a reasonable number of granulocytes. The onset of drug fever, rash and delirium on the seventh to the tenth day is obviously not caused by pneumonia, and the pulse usually remains slow.

When a patient suffering from chronic asthma develops fever, it is often well to administer some sulfonamide, for sputum examinations in such cases invariably reveal the presence of pathogenic bacteria. Such therapy should be in addition to the usual asthma treatment, for without the supplemental action of the latter, these patients do poorly. The same line of attack in those with fever and congestive heart failure often leads to the success of otherwise inefficacious cardiac therapy. Chemotherapy with the sulfonamides in such cases, however, should not be continued if there is no improvement in twenty-four to forty-eight hours. If the temperature shows an immediate response, treatment should be carried on for about five days.

Dr. Finland discussed "influenza" and its complications. During the epidemic a year ago, a virus identified as influenza A was isolated in many cases, and a measurable antibody titer found. There were an unusual number of staphylococcal pneumonias of marked severity. These patients were usually sick about two or three weeks, and although there was a tendency for the formation of lung abscesses and empyema, recovery was the rule. On the other hand, there were patients who had a sudden recurrence of signs and symptoms shortly after their apparent recovery from the "grippe," with severe cyanosis, cough, inability to raise sputum and sudden death. The pathological findings in these patients were similar to those of influenza patients of World War I. It is impossible to determine how many of these changes are attributable to the virus infection and how many to the superimposed pneumonia; therefore, the etiologic agent of the latter should be treated, since there is as yet no adequate therapy for the virus of influenza. The question is often raised whether all influenza patients should be treated with sulfonamides, but Dr. Finland is not in favor of such a procedure except in epidemics in which there are many pulmonary complications and persistent fevers, and bacteria are cultured.

In conclusion, Dr. Finland answered questions. Fastness to the sulfonamide drugs is probably not a common or significant occurrence. All susceptibility to these drugs is relative, and if fastness is developed in any case, there is no use in attempting to substitute one drug for another, for these cases develop fastness to all.

No truly characteristic temperature chart is caused by "drug fever," but there is usually not a commensurate increase of pulse and the patient does not look so ill as the chart indicates. Such a fever seldom occurs in less than a week, except rarely with sulfathiazole or when the patient fails to report previous treatment by his own physician.

Vaccines do not seem to offer much hope. There is no sound basis for their use as a protection against pneumonia, for there are about sixty strains of the pneumococcus and forty of the streptococcus, besides an unknown number of staphylococcal strains. This mitigates against the inclusion of all strains, and anything less could not be considered adequate protection against any given case of pneumonia. Furthermore, staphylococcal and streptococcal vaccines afford only a temporary immunity, and the pneumococcus cultured from the throat is usually not the responsible organism in lobar pneumonia and therefore cannot be used as a criterion of what to include in a vaccine. The use of vaccines against influenza, however, may be important in the future. At present, vaccines containing influenza A and the virus of dog distemper protect the ferret but are only suggestively valuable in man. Their efficacy appears to vary from place to place but may be increased in the future.

Serum therapy of pneumonia has not been entirely supplanted, but is used in specific cases, namely, in patients over fifty years of age, in those who suffer from chronic alcoholism, particularly delirium tremens, and in those who fail to respond to chemotherapy. Dr. Finland issued a caution against a false sense of security on the basis of a falling temperature in patients treated with sulfapyridine, for this drug has an antipyretic as well as bacteriostatic

effect. The response to sulfathiazole and sulfadiazine is slower, so far as the temperature chart is concerned, but the patient invariably feels and looks better even before there is any temperature response. In children, all drugs are apparently efficacious and are less toxic. In fact, the mortality from pneumococcal pneumonia in infants and children has decreased from 30 to 3 per cent since the advent of chemotherapy, and serum is seldom necessary.

BOOK REVIEWS

Trauma and Disease. Edited by Leopold Brahdy, M.D., and Samuel Kahn, M.D. Second edition. 8°, cloth, 655 pp., with 13 illustrations and 13 tables. Philadelphia: Lea and Febiger, 1941. $7.50.

This book is a symposium on the relation of trauma to diseases of the various organs. The many authors are well qualified to write on their subjects. Such names as Paul White, Hugh Cabot, George Blumer and Elliott Joslin give a note of authority that a single author could not begin to achieve.

A great many unjust settlements for injuries are made largely because some authority such as this book has not been consulted by those who make the final decisions. Past decisions are unreliable in establishing liability or fair compensation. The new knowledge of disease, based on the study of pathology and physiology, calls for a new legal interpretation of disease as related to trauma. In this development, the present work will be a valuable aid.

Each organ or system of the body is considered separately, and the material is arranged so that reference is readily made to any desired subject. The book should be of great value to those members of the medical and legal professions who deal with compensation cases.

Cardiac Classics: A collection of classic works on the heart and circulation, with comprehensive biographic accounts of the authors. Compiled by Frederick A. Willius, M.D., and Thomas E. Keys, M.A. 4°, cloth, 858 pp., with 102 illustrations. St. Louis: The C. V. Mosby Company, 1941. $10.00.

The authors have performed a useful service for the medical profession, especially for those interested in the development of the knowledge of cardiovascular disease, by assembling in one volume some of the more important original contributions. This book begins with a brief account of the influence of certain cardiac classics on the development of modern cardiology. The introduction is followed immediately by a complete transcription of William Harvey's classic treatise on the circulation of the blood, as translated by Robert Willis, of Barnes, Surrey, England, in 1847. The extensive quotation from Harvey is followed by contributions in whole or in part from fifty other authorities, ending with Sir James Mackenzie, Sir William Osler, James B. Herrick and Oliver Wendell Holmes ("The Stethoscope Song — A Professional Ballad").

No two persons would agree in every detail concerning the value of many of these contributions. The reviewer would like to have seen something quoted from several of the more important earlier writers not included here, such as Lower, Bonetus, Vieussens and Lancisi, but he has been compensated by an opportunity to become acquainted with several authors whose works he had not previously read.

One of the helpful and interesting parts of the book is the collection of brief biographies preceding each quotation. Among the other authors quoted whose names and works are best known are Malpighi, Hales, Senac, Morgagni, Auenbrugger, Heberden, Withering, Corvisart, Laennec, Hope, Stokes, Flint, Roger, Steell, Broadbent, Einthoven and Keith.

At the end of the book are short tables giving the correlation of these classics with other contemporary historical events and a list of biographical references. A good many interesting illustrations are included, such as the pictures of some of the authors themselves, occasional title pages, pulse tracings, Laennec's stethoscope, and drawings of normal and pathologic hearts.

Communicable Disease Control: A volume for the health officer and public health nurse. By Gaylord W. Anderson, M.D., and Margaret G. Arnstein, R.N., M.A., M.P.H. 8°, cloth, 434 pp., with 13 tables. New York: The Macmillan Company, 1941. $4.25.

This volume, which furnishes concise information in a clear form on the subject of communicable-disease control for the community, is a very valuable addition to the literature.

The chapter on the infectious process, in which an analogy is drawn between the effect of forces acting on a block in the physics laboratory and the forces of infection and resistance, is clearly expressed without recourse to unfamiliar terms, and gives one of the clearest presentations available in the literature.

General control measures are discussed, embodying the principles without undue verbiage. Legal basis for control is cited, and the various administrative agencies for control are briefly reviewed. There is an excellent chapter on the role of the public-health nurse, and one on the home care of patients with communicable diseases.

The book is consistent in discussing individual diseases. The pattern is always obvious, and one can immediately find the desired information under its appropriate heading for each disease discussed. The order is: occurrence of disease, the etiologic agent, the reservoir of infection, escape from the reservoir, transmission, entry and incubation period, susceptibility, control methods and minimizing ill effects.

The volume, which should be in the hands of every public-health official and nurse, will be a useful addition to the library of every general practitioner.

Rheumatic Fever in New Haven. Edited by John R. Paul, M.D. 8°, paper, 176 pp., with 22 tables and 45 charts. Lancaster, Penn.: The Science Press Printing Company, 1941. $1.00.

This is an epidemiologic study of rheumatic fever. Although the etiology of this disease is obscure and there are no definite tests available for diagnosis, much can be learned of the public-health aspects of rheumatic fever by the statistical method. The incidence of the disease was calculated from hospital admissions in the three large hospitals in New Haven. The active cases made up 1.2 per cent of the admissions to the medical services. The incidence of rheumatic heart disease was found to be somewhat lower among a group of relatively well-to-do students of Yale University, but the factor of poverty does not seem to have so important a predisposing role in determining the incidence of rheumatic heart disease as it does in tuberculosis. The disease is distributed fairly evenly among people of different nationalities. The clinical entity of rheumatic fever is rarely precipitated in a normal person as a result of his first contact with the infectious agent. The author believes that the infant must grow up to be a rheumatic. Poverty and crowding, according to this study, do not appreciably enhance the prevalence of rheumatic fever.

(Notices on page ix)